# INTERNATIONAL RECORD OF MEDICINE

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## & GENERAL PRACTICE CLINICS

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### SYMPOSIUM ON WHIPLASH INJURIES


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FELIX MARTI-IBAÑEZ, M.D., Editor

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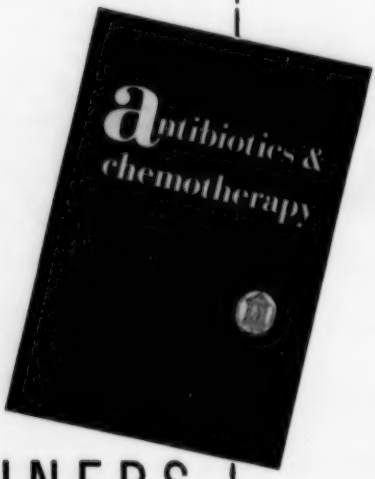


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VOL. 169 NO. 1 WHOLE NUMBER 2875 JANUARY 1956


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1. Howell, T.H.; Harth, J.A.P., and Dietrich, M.: Practitioner *173*:172.
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## SYMPOSIUM ON WHIPLASH INJURIES*

# Introduction

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A whiplash injury is the damage sustained by the neck structures when the body, in propulsion, comes to a sudden stop or when the body is suddenly propelled forward and the head is thrust forcibly forward, and/or backward, and/or to either side. This often occurs in automobile collisions, particularly rear-end collisions. It also occurs in many other types of accidents or falls in which there is a sudden jolt of the body and the head swings to and fro. One might say then that the head becomes the tail of a crack-the-whip motion.

There is much to be learned about the mechanism of the stresses in the injury, the structural damage to the neck, the resulting signs and symptoms, the therapeutic measures indicated, the possible safety measures needed, the residual disability, and the possible need of legal measures in license control for injured pilots and drivers. These and other factors are presented by the various experts on the panel.

With the increasing number of more powerful automobiles, further congesting our already congested highways, there are more and more collisions, many of the rear-end type in which the whiplash injury is so frequently encountered. It is not uncommon in freeway accidents to see from three to fifteen automobiles telescoped in collision. The problem of the whiplash injury is therefore of national importance for the safety of our populace. It is also a personal problem, since each of us as drivers or pedestrians are involuntarily playing a dangerous and sometimes fatal game of crack-the-whip with our necks.

At this time, we are happy indeed to have for our Moderator the former Surgeon General of the United States Navy, who so capably directed, during World War II, the excellent medical care of the Navy and United States Marine Corps under greatly varying conditions over the entire world. It is with great pleasure that I present to you our Moderator, Admiral Ross T. McIntire.

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# Opening Remarks

*Vice Admiral Ross T. McIntire, M.C., U.S.N. (Ret.)*

In considering whiplash injuries to the cervical spine and associated structures, the members of the panel will comment on the various aspects about which they are outstanding in their fields. With the experience gained in seeing firsthand a great number of these types of injuries, they will contribute, I am sure, constructive information that will be of great use not only to doctors but also to those in the legal profession.

It may seem strange that a retired Surgeon General officer of the Medical Corps of the Navy should act as moderator for this panel. Perhaps the reason is that I have been associated with naval aviation over a great number of years. Following World War I, the Navy instituted the launching of planes from the decks of battleships and cruisers by the catapult method. The mechanics of this is well understood now, but, in the earliest days, the pilot was not properly protected. Consequently, the violence to the cervical spine in catapulting was great enough to cause a blackout for a few seconds and accidents occurred that were undoubtedly due to the whiplash effect. Because this was recognized quickly, we were able to provide a protective headrest for the pilot, with adequate shoulder harness, so that no further damage to the neck and associated structures occurred and there were no further blackouts. Also, when "hitting the cables," in carrier landings, there may be a sharp forward thrust, whipping the head and neck.

The pioneer work that was done because of catapulting made aeronautical constructors very conscious of the need to protect the pilot against violence of external forces; since then the pilot has always had proper support for torso, neck, and head.

As many of you know, I have been vitally interested in the field of rehabilitation over a great many years. During World War II, it was necessary to establish rehabilitation services in many parts of the country. We soon found out that the automotive equipment used by Navy personnel was causing many injuries to the head and neck. I am sure that injuries of the whiplash type were not recognized or properly treated.

It is a splendid thing to know that men such as Dr. Billig and his associates, who have contributed so much to our knowledge of this particular type of injury, are doing research in this field.

# The Mechanism of Whiplash Injuries

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Injuries to the neck and its component structures as a result of forceful motion in various directions have long been recognized. Recently, articles concerning complaints of head, neck, and arm symptoms following "jerking" of the neck in automobile accidents, particularly rear-end collisions, have appeared in the literature. The military services have also had to face this problem as a result of jeep accidents, the sudden thrust in catapult launching of aircraft, and the sudden forceful braking of aircraft when "hitting the cables" in carrier landings. It has been recognized that the motion of the head and neck in one direction, with the body as a base, is often quickly followed by a sharp motion in the opposite direction, and hence the term "whiplash" injuries of the neck has appeared. The whole mechanism is similar to "cracking the whip." In this case, a knot tied to the end of the whip represents the head, the rest of the whip the neck, and the handle or base, the body. In this regard, the effect of seat belts and shoulder belts in automobiles is being carefully investigated. As yet there is no concerted opinion on the problem, but great care is being taken to estimate all the factors involved and their possible correlation with whiplash injuries.

The various forces that may be transmitted to the neck in whiplash injuries consist of compression, distention, bending, shearing, and torsion. With the head, body, and carrier all traveling at a set rate, there are no abnormal forces transmitted to the neck. But, if the forward motion of the body (together with the carrier) suddenly stops, the head, owing to its momentum, continues forward and produces an abnormal thrust to the neck. If the body (together with the carrier) is suddenly accelerated in forward propulsion, as in rear-end collision while parked or in catapult launching, the head, owing to its inertia, is whipped backward in relation to the body, producing an abnormal backward thrust to the neck. In addition, the head may then swing on the neck in rebound, in the opposite direction, representing the lash component of the whiplash. If the head and neck are turned at the time, abnormal torsion forces will be transmitted to the neck.

The mechanical structures of the neck are so constituted that the neck can tilt forward, backward, and sideward and rotate by means of gliding motion in the facet joints that are set one on each side between each of the cervical vertebrae. The motion in the facet joints is limited by joint ligaments surrounding the whole of the joint circumference. The extent of motion in the neck as a whole is limited by fasciae and ligaments.

If the head and neck are forcibly swung forward, either in the whip or lash component, past the limit of motion, some of the following injuries may be sustained:

A. Compression fracture of one or more cervical vertebrae, with varying degrees of loss of height.

B. Compression damage in multiple ruptures of the delicate internal hydraulic

structure of one or more of the intervertebral discs (90+ per cent water!), with permanent loss of height resulting in altered mechanical alignment of the cervical spine (reverse curve). With loss in height of the disc space, there is a teetering toward each other of the adjacent vertebral bodies and a concomitant teetering apart of the posterior structures, with the facet joints as the fulcrums. This causes abnormal distention, with resultant tightening compression forces on the posterior structures (ligaments, etc.) through which the peripheral and autonomic nerves must pass. This may result in sensory, motor, and sympathetic nerve manifestations in both the cervical and brachial plexuses. Frequent findings on the electromyograph in the innervated muscles are polyphasic motor units, owing to nerve fiber compression damage, and fibrillation, owing to complete interruption of continuity of some of the nerve fibers in the affected nerve. The polyphasic motor units may be observed within a few hours after the injury, but it takes five to seven days before the fibrillation following complete interruption of the motor nerve fiber can be shown. With electromyograph tests of all muscles supplied by the cervical and brachial plexuses, it is possible, through knowledge of differential nerve root distribution to the muscles, accurately to localize the lesions. Not uncommonly, the abnormal nerve compression of the cervical sympathetics on one side causes excessive dilation of the pupil of the eye on that side (opposite of constriction of pupil due to the interruption of stimulus in Horner's syndrome), with symptoms of blurred and distorted vision.

C. Compression may cause damage to the lips or margins of the vertebral bodies. Frequently, the margin is mushed outward to resemble a long standing spur. Figure 1 shows a lateral cervical roentgenogram taken of a prominent surgeon's neck (prior

Fig. 1. A lateral cervical roentgenogram taken prior to injury.

FIG. 2. A lateral cervical roentgenogram taken of the same person following a severe whiplash injury.

to injury) while acting as a subject in teaching his technician proper roentgen-ray technique. Figure 2 shows the same neck (of this 50 year old physician) following a severe whiplash injury to it when struck forcibly from the rear in an auto collision. The mushed-out lip margins of the bodies at C6 and C7 and the loss of height of the C6-C7 intervertebral disc are results of the lash phase (forward rebound) of the whiplash; by comparison with figure 1, it is clear that they are *not* the result of "an old arthritis of many years' standing." Figure 2 also shows marked posterior subluxations of C2 on C3 and C3 on C4, caused by the initial whip (backward) phase of the whiplash motion.

D. Shearing and bending force fracture of the odontoid process. If the patient survives initially, this type of fracture usually heals with proper immobilization.

E. Distention and torsion and bending force avulsion of the posterior portion of the facet joint ligaments with: (a) forward subluxation of one or both sides of one or more vertebrae on the adjacent underlying vertebrae (Thomas collar immobilization in position of reduction is indicated); (b) dislocation of one or both sides of one or more vertebrae on the adjacent underlying vertebrae. (The hazard of spinal cord damage is a pertinent issue and immediate reduction is imperative, using, as indicated in the particular case, decompression and traction (Crutchfield tongs) reduction, followed by immobilization and later fusion.

F. Shearing and bending and compression fractures of the laminae and/or facets. These are often difficult to visualize on the roentgenogram. Stereoscopic and oblique projections have been suggested and, recently, B. F. Boylston, of Houston, has suggested an anterior-posterior projection with the head and neck maximally rotated and tilted to the side. Immobilization is indicated.

G. Distention force nerve root avulsion. See previous discussion of electromyograph under point 2.

H. Herniated intervertebral disc.

I. Fracture or ligamentous avulsion of spinous processes (uncommon).

If the head and neck are forcibly swung backward, either in the whip or lash component, past the limit of motion, some of the following injuries may be sustained:

A. Distention force avulsion of the anterior spinous ligaments from the lips or margins of the bodies (with or without bony avulsion).

B. Distention and torsion and bending force avulsion of the anterior portion of the facet joint ligaments with: (a) posterior subluxation of one or both sides of one or more vertebrae on the adjacent underlying vertebrae; (b) dislocation of one or both sides of one or more vertebrae on the adjacent underlying vertebrae.

C. Shearing and bending and compression fracture of the laminae and/or facets.

D. Distention force nerve root avulsion.

E. Shearing and bending fracture of the odontoid process.

F. Fracture of spinous processes (uncommon).

If the head and neck are tilted or rotated to the side or if the striking force is more to the side at the time of injury, the exact position of the head and neck and direction of force will determine which of the above injuries is most likely to occur. Torsion forces in combination with sideward tilt may frequently initiate unilateral subluxations or dislocations.

Initial symptoms immediately following injury may be minimal. One or more of the following complaints are frequently voiced: "jerk of the neck" in either the forward or backward movement, depending upon which of the movements focused the neck to the patient's attention and not upon which motion came first, "dizziness," "dazed," "nausea," "poorly coordinated," "generalized numbed feeling," "blurred and/or distorted vision," "pain and numbness shooting into head, arms, or down back from neck."

Twenty-four hours after injury, the neck usually begins to stiffen, muscle spasm can be detected, and the individual may complain of pain in the head or outward to the shoulder and arms. Owing to the immobilization from the muscle spasm and strain contracture of the fasciae and ligaments, diagnostic roentgenograms at this time may not show the presence of subluxations, so it may be several months following injury before the subluxations become demonstrable.

The peripheral motor, sensory, and autonomic nerves traverse the narrow cervical intervertebral canals and then pass through ligaments and fascial planes so that any disturbance of mechanical alignment may cause compression of these nerves, with radiation of motor, sensory, and autonomic nerve signs and symptoms to neck, head, eyes, and arms and hands. Gross reflex changes in the arms are not usually discernible; however, one may on occasion notice fibrillary twitchings in some muscles, indicating abnormal motor nerve fiber irritation stimuli.

In treatment, distention traction (with head halter or "tongs") is frequently used. In the absence of dislocation, if there is still a possibility of subluxations being present, it is inadvisable to use such traction to transmit distention force to the facet ligaments, since the first consideration is to allow the facet joint ligaments to tie down in healing and to minimize the danger of a permanently recurrent sub-

FIG. 3. Permanent subluxations present three years after injury in a case in which extended distention traction with head halter has been used.

luxation. Figure 3 shows the permanent subluxations present three years after injury in a case in which extended distention traction with head halter was used.

Careful lateral roentgen-ray projection views should be taken in full forced forward, neutral, and full forced backward thrust positions of the head and neck and a Thomas collar fitted to hold the head and neck in the position that maintains reduction of the subluxations. After the Thomas collar has been worn for sufficient time to allow maximum possible healing of the joint ligaments, as determined by repeated lateral roentgenograms taken in the full forward thrust, neutral, and full backward thrust positions of the head and neck, the time then comes to loosen the fascial and ligamentous contracture resulting from the injury of the strain at the time of the accident as well as from the Thomas collar immobilization. This may be done by gentle, progressive accumulative loosening through torsion stretching exercises performed several times to each side three times daily, being extremely careful not to place a strain on the facet joint ligaments. These exercises are done as forced rotations of the head and neck, carried each time just a little way past the restricted limit so as to register a net gain each day. The frequent complaints of headache and facial neuralgia following these whiplash injuries to the neck may thus be relieved. The autonomic blocking agents, methantheline bromide and chlorpromazine, or local anesthesia injections at the cervical ganglia are useful in controlling symptoms.

Fractures, particularly those in the facet joints, tend to heal very slowly and have as sequelae local traumatic arthritic changes. The intensity and frequency of signs and symptoms will govern the decision whether or not to advise cervical spinal fusion.

# The Autonomic Nervous System in Whiplash Injuries

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Whiplash injuries generally fail to respond to conventional treatments, although the neck and shoulder pain and stiffness are easier to relieve than the associated autonomic system dysfunctions. Office traction and physiotherapy, including diathermy, infrared therapy, iontophoresis, ultrasonics, and massage, as well as felt collars and medications, should be considered only as adjunct procedures. The vasodilators, the so-called autonomic blocking agents, and the muscle relaxants are by themselves of only slight and transitory value. The same applies to the vitamin $B_{12}$, the vitamin B complex, ascorbic acid, and other vitamins; a high protein diet; analgesics; and hormones, including androgens, estrogens, and the corticosteroids. Chlorpromazine and related preparations have not been adequately evaluated. Far more important is home therapy: repeated day and night traction, warm baths, contrast sprays, hot moist packs, gentle massage, mild counterirritants, indirect heating, and exercises against increasing resistance. Ethyl chloride sprayed on trigger points or local injections with 1 per cent novocain, hydrocortisone, and hyaluronidase are of benefit. It should be emphasized that indiscriminate manipulations and traction may aggravate the injury.

It is unfortunate that attorneys, insurance adjustors, and the courts are placing increasing emphasis on positive roentgenographic evidence of fractures or dislocations as a criterion in evaluating an injury. Other participants in this symposium (Billig and Morrow) have discussed bone injuries and referred to the increased positive findings when roentgenograms are taken with the cervical spine in flexion. Another improvement, presented at the 1954 meeting of the American Radiological Association, is to show the spine in traction roentgenograms. Planograms may disclose minute fractures that are not apparent on routine films. Myelograms may be required for verification of disc herniation. Negative roentgen-ray findings, as well as negative electroencephalograms and negative electromyograms, are in the same category as negative electrocardiograms in the presence of myocardial damage There is an urgent need to increase the clinical and experimental evaluation of these procedures and to reduce the cost of roentgen-ray and other laboratory procedures so that repeated examinations can be made and new techniques utilized.

A major factor in the production of pain, muscle spasm, and disability in whiplash injury is "irritation" of the cervical nerve roots. Frequently, wear and tear has produced pre-existing disc degeneration and hypertrophic arthritis, with intervertebral narrowing of the foramen. The injury then acts as a precipitating factor, causing pressure on the emerging nerve roots and producing the cervical disc syndrome, or "root neuritis" picture. Altered sensation, spasm, and stiffness in the regional muscles may be the dominant elements.

A second factor comprises the tearing, stretching, and bruising of the musculo-

ligamentous structures of the neck and shoulder region. As in any traumatized tissue, there is vasodilation of the arterioles, venules, and capillaries. The red blood cells are lightly covered with a sticky protein substance and become agglutinated to form a sludge. This sludge delays the blood flow in the already constricted vessels. The capillary endothelium, being deprived of oxygen, permits plasma to pass easily through the capillary walls into tissue spaces. The slow, sticky sludge then tends to settle in the vessels and to form elongated gelatinous masses that become attached to the vein walls. Such a mass may become the nidus for the formation of a thrombus and a focus of irritation to stimulate pain.

Pain is essential for life and function. It can generally be considered as a signal of danger or damage to the body. Precisely how various kinds of pain arise and how they affect the higher levels of the nervous system has not been clarified. Pain impulses are carried centrally in both somatic and sensory fibers. Reflex mechanisms in the sympathetic nervous system have been postulated in plexuses about the vessels, in sympathetic ganglia, and at the highest level in the diencephalon. By activating efferent sympathetic nerve fibers, the body attempts to minimize pain and trauma through reflex vasoconstriction and increased capillary permeability. There is also an indirect effect on the cardiorespiratory center, on various glands, and on body fluids.

Another theory for the production of pain is that the internuncial system within the spinal cord is stimulated. Repeated excitation of these intercommunicating neurons maintains the cord active at levels overlapping the anatomic level related to the injury. This stimulation is then discharged through lateral (autonomic) horns or through the anterior horns, producing motor effects such as muscle spasm, with additional pain.

When this overactivity of the cord is discharged through the autonomic connections, autonomic reactions are provoked. Other mechanisms involved in the production of these varied and "distant" dysfunctions are cerebral, spinal, and the so-called "autonomic concussion." Gross injuries to the head and skull fractures will not be discussed here, but minor concussions and the postconcussion syndrome are pertinent to the whiplash problem. The head may strike against the windshield or some other part of the car, causing cerebral injury. When the movement of the head is suddenly stopped without striking anything, the brain, floating as it were in its cerebrospinal fluid, continues its momentum until it strikes the skull and produces a contrecoup lesion. Even without fracture of the skull, brain contusions, microscopic hemorrhages, and altered circulation in the small vessels occur. This, in turn, causes injury and degeneration in the nerve cells of the area, such as in the vestibular portion of the eighth nerve and the cardiac and vasomotor centers. The hypothalamus is also stimulated by injured neck and shoulder structures.

A new term—"autonomic nervous system concussion"—can be coined to describe damage to the cerebral sympathetic ganglia and their connections. Minute hemorrhages, edema, and irritation of the cervical ganglia can be determined only indirectly through their effects on other structures. More attention should be paid to the "indirect" effects of autonomic injury. A variety of vague disorders, too readily labeled (or libeled) "functional" or traumatic neuroses, are better under-

stood after studying the functional anatomy of the cervical autonomic nervous system. Headaches, dizziness, syncope, memory lapses, inability to concentrate or to solve simple problems, and personality changes may all be caused by altered cerebral blood flow, by stimuli from the injured cervical structures, or by the post-concussion syndrome.

Vasomotor disorders, with cold hands and feet, gross tremors, excessive axillary sweating, oversensitivity to environmental stimuli and tensions, tachycardia, precordial distress, and hyperventilation are all part of the picture. More attention should also be paid to the possible effect of the hypothalamus-pituitary-adrenal mechanism in activating peptic ulcers, hyperthyroidism, arthritis, diabetes, asthma, hypertension, and other "stress" diseases.

Cervical sympathetic blocks are of value in a variety of pains and disabilities of the neck, shoulder, and upper extremities, including whiplash injuries. Instead of using stellate blocks, I prefer to block the middle cervical sympathetic ganglion through an anterior, paratracheal approach. Injections consist of 1 or 2 per cent novocain or some other short-acting anesthetic. If the patient is hospitalized, a fine polythene tube is inserted anterolaterally through the sternocleidomastoid muscle. Twenty ml. of 1 per cent novocain is then injected into the tube every two to three hours. Traction and other forms of treatment can then be undertaken.

In the victim of a whiplash injury, cervical sympathetic blocks provide increased blood flow to the extremities and reduce pain, thereby permitting exercises and other rehabilitation procedures. A progressive increase in the movement of muscles, ligaments, and joints promotes healing and a return to normal function. Cerebral vasospasm and "distant" autonomic dysfunctions are also indirectly benefited.

# Body Functions and Controls in Whiplash Injuries

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In 1908, in his Liverpool laboratory, Sir Charles Sherrington, then a physiology professor, demonstrated a new finding to an assistant, Rudolph Magnus, a pharmacologist of Utrecht. Turning the head of a decerebrate animal, he pointed out that rigidity of the animal's muscles increased on the side toward which the head was turned and diminished on the opposite side. Sherrington remarked to Magnus that the phenomenon deserved further study.

Magnus continued the investigation for 16 years and, in 1924, published his findings in a book entitled *Körperstellung*, literally meaning, "body posture." This book developed the first clear-cut analysis of the three-dimensional problem of postural reflexes. These are: (1) *Local static reactions* arising primarily from gravitational stimuli in the muscles themselves. (2) *Segmental static reactions* arising from the effects of moving one extremity on the opposite extremity. Nerve impulses from the moving muscle act on fellow muscles of the same segment on the opposite side. (3) *General static reactions* arising from the sensory organs of the inner ear and from the sensory neuromuscular spindles in the neck muscles.

Additional sources of sensory impulses that initiate reflex movements of importance in maintaining balance and postural tonus are *vision* and *touch*.

The general static reactions and vision are the functions most likely to be affected in whiplash injuries to the neck and head. The reflex mechanisms responsible for orienting the position of the head in space are the tonic neck reflexes and the labyrinthine righting reflexes. These are independent of movement or acceleration. Acceleratory reactions come from the semicircular canals.

Tonic neck reflexes arise from the rich supply of sensory receptors in the neck. When the muscles or tendons are stretched, as in tilting the head to one side, the receptors are stimulated and the righting reflex is actuated. Injuries to muscles and tendons tend to impair this important balance mechanism. Also, residual neuromuscular hypertension, or stiffness, arising as a secondary effect of injury, damages the tonic neck reflex action.

The tonic neck reflexes act also in adjusting the tone of postural muscles throughout the body. A change in position of the head affects the alignment of the body. In athletic skills such as springboard diving and gymnastic tumbling, the effect of a slight turn of the head in altering body movement is well known. Slight asymmetrical tensions in the neck, as when the head is drawn back or to the side, make tasks requiring accuracy highly difficult. Injury to nerves, muscles, and tendons of the neck can seriously decrease the quality of performance of highly skilled industrial workers or athletes.

The neck righting reflex serves to restore bodily alignment and correct balance

if it is lost, as in stumbling forward. Once the neck has been extended in response to other body righting reflexes, the neck muscle and tendon receptors are stimulated and reflex muscular adjustments tend to bring the body into a horizontal position to follow the head. The righting reflex thus prevents falling by halting forward momentum and preserving balance. The neck righting reflex is usually accompanied by a grasping reflex in which the fingers and thumbs are brought together. The tendency of patients with neck injuries to fall easily and to drop things is probably related to an impairment of the neck righting and grasping reflexes.

Labyrinthine righting reflexes have a stronger influence than the tonic neck reflexes in bringing the body as a whole into the upright position. When the head is moved, tiny particles of calcium called "otoliths" drift from one part of the wall of the labyrinth of the inner ear to another. The pressure of the otoliths upon the sensory nerve receptors provokes impulses that produce the sensation of position. Only slight stimuli are necessary to evoke reflexes that bring the head into a horizontal position. The change in head position excites the tonic neck reflexes, and together they keep the body erect. Injury to the labyrinthine righting reflex makes it difficult for the patient to stand erect either with his eyes closed or in the dark.

Acceleratory reactions of the semicircular canals of the inner ear have nothing to do with the labyrinthine righting reflexes. The acceleratory responses depend on movement. Movement agitates the fluid of the inner ear canals, producing a sense of motion and the ability to make orientations and reorientations in space. These responses are called "statokinetic reflexes" and set up tensions and reactions leading to further adaptive movement. They assist in coordination and balance during motion.

A brief period of whirling is enough to affect the balance of most normal people. While whirling, the fluid of the inner ear canals is agitated and continues in motion when the whirling stops, giving the sense of continued motion. Attempts to reach an equilibrium with a false sensation of motion result in failure to stand erect or to move with precision. These organs are so sensitive that if they are damaged, even though visual and other sensations are intact, the patient is continually losing his balance and struggling to regain it.

Visual impressions are important in maintaining an erect and balanced posture and in performing tasks requiring judgment of distance and speed. The importance of keeping the eyes on the ball in catching and striking a baseball is well known. In striking a golf ball, however, it is probably the neck and labyrinthine reflexes that deflect the stroke when the eyes are lifted during the swing. Eye movements and poses do, to some extent, serve to initiate and direct the stance and movement of the body. Also, the eyes assume compensatory poses with changes in stance.

Some contraction and relaxation of the iris of the pupil is observed with a slight shifting in balance. In an off-balance position, there is a minute dilation of the pupil. The pupil returns to the normal constricted size when balance is recovered. This phenomenon was brought to my attention by Alex Morrison, a golf professional, and has not heretofore been described in print.

Considerable pupillary control is exerted by the cervical sympathetic nervous system. Paralysis of the sympathetic nerves of the eye results in constriction of the

pupil, slight retraction of the eyeball, and narrowing of the space between the eyelids. Stimulation of the cervical sympathetic nervous system has an adrenergic effect in dilating the pupils. In certain neck injuries, Billig has demonstrated that head turning evokes pupil dilation when the head is turned to the injured side. Usually the pupil on the injured side responds, but occasionally both eyes dilate. The mechanism eliciting this response is apparently a mechanical stimulation of a cervical sympathetic nerve made irritable by injury. Since the cervical sympathetic nerves arise from the ganglia in front of the transverse processes of the second, third, and fourth cervical vertebrae, and are embedded in the fasciae and muscles of the neck as they extend into the head, it is entirely feasible that muscular or fascial contractures could cause pressure stimuli to the cervical sympathetics, resulting in pupil dilation when the head is turned. It is further possible that damage to the cervical or stellate ganglion, resulting from neck injury, is exacerbated by head turning.

### Some Facts about the Food and Drug Administration

• The FDA has 207 inspectors, including 15 import food and drug examiners, working throughout the nation out of 16 district offices.

• All together, the FDA employs about 1033 persons, only a few more than in 1940 when the new Pure Food and Drug Law became effective.

• Approximately 1400 legal actions are taken annually by the FDA against violators of the law.

• The financial appropriation for 1955 was $5,100,000, or $500,000 less than in 1953. This is about 3.25 cents per person.

• The FDA is responsible for commodities costing more than $50 billion in domestic commerce and $3 billion in imports annually, for which products the public spends approximately one fourth of the average family income.

• There are about 96,000 processing and manufacturing plants and warehouses, not to mention thousands of retail establishments, handling products subject to the food and drug law. About 9000 plants are inspected annually.

• The FDA uses modern scientific methods to enforce the law. It was one of the first agencies to utilize scientific crime detection techniques.

• A series of exclusive editorials on the work of the Food and Drug Administration will be published in International Record of Medicine and General Practice Clinics, Antibiotics & Chemotherapy, and Antibiotic Medicine, journals of MD Publications, Inc. The first of these editorials appear on page 36 of this issue.

# Surgical Anatomy of Whiplash Injuries

*James Morrow, M.D.*

As aids in recognizing sites of possible injury to the bony structure of the neck and explaining why soft-tissue injuries are so often associated with bone damage in this area, the accompanying figures illustrate the anatomic pathology of various types of injury.

It will be noticed, in figure 1, that there is a loss of the anterior curvature of the cervical spine. It is well recognized that, when the muscles of the neck become rigid as a result of injury or other factors, this anterior curvature is frequently lost; and this finding is almost universally demonstrated in the early phases of whiplash injury to the cervical spine or the neck structures. This roentgenogram is of a 31 year old woman who was injured in an automobile accident and sustained a so-called whiplash type of injury four months before this picture was taken. There is no evidence of a pathological bone condition in this particular case but, beneath the hyoid bone, there is an area of greater density, representing the shadow of an enlarged thyroid gland, since this woman had a definite hyperthyroidism influenced by strain or emotional factors at the time of the accident. Hyperthyroidism, therefore, can be associated with whiplash injuries. Whether it is an aggravation of a preexisting condition or a direct result of the accident or of the emotions induced by the accident are questions to be considered in each case. People with enlarged and acutely active thyroids tend to lose the anterior arch of the cervical outline. In addition to the problem of hyperthyroidism, in this case, besides the usual seven, there is an auxiliary, or eighth, cervical vertebra. People with an anatomic abnormality of this nature tend to lose the normal anterior curvature of the cervical spine.

It is recognized that soft tissues in the neck may be injured in whiplash injuries; such injuries frequently predominate in causing pain, even when there is no demonstrable injury to the cervical vertebrae nor any dislocation or subluxation of the body or injury to the intervertebral discs. Figure 2 is a drawing of the cervical vertebrae showing the course of the vertebral arteries, the right and left both passing through the lateral portions of the cervical spine between the lamellae. It is interesting to note how this vessel arcs over the second vertebral body before it courses past the atlas and then enters the occiput. Injuries to the higher cervical vertebrae can damage the vertebral artery, with subsequent hematoma and pressures that unquestionably are associated with the persistent headaches that follow whiplash injuries to the neck. It is obviously difficult to make such a specific diagnosis, but there is no reason to conclude anatomically that such a condition does not exist and that the artery involved could not have been so injured.

Injuries occurring in the upper portion of the posterior neck structures involve not only the muscles attached to the first and second vertebral bodies (the rectus capitus and the inferior oblique capitus) but also the veins and plexus of veins, to the extent that they likewise become injured and lose blood from their lumen. As a result, hematoma are formed, which give rise to pressure symptoms and painful sensations not only in the posterior upper neck but also extending under the scalp

FIG. 1. Roentgenogram showing the loss of the anterior curvature of the cervical spine.

covering the posterior base of the skull itself. The aspiration or withdrawal of blood gives prompt and definite relief.

One of the commonest soft-tissue injuries is to the sternocleidomastoid muscle because of the strain placed upon it, which ruptures some of the small vessels and muscle fibers and produces hemorrhage within the muscle. These hematomas sometimes reach an astonishing size. The patient who has received injury to this particular muscle will frequently complain of pain behind the ear on the involved side or even extension of pain into the scalp behind and above the ear. An additional problem is that of nerve distribution. The cutaneous colli nerve branches across the middle portion of the sternocleidomastoid muscle and the minor occipital nerve rises to the ear and into the scalp; the greater auricular nerve distributes its fibers at the angle of the jaw near the ear. When the sternocleidomastoid muscle is sufficiently injured, radiation along these nerve trunks develops into a painful neuralgia, thereby further complicating the soft-tissue injury.

In the chronic states following whiplash injury, small neuromas can form in these nerves and create a painful "trigger point" mechanism. Again, a thickening of the muscle fascia may eventually occur, thus creating still further problems by limiting movement. It is my own opinion that the injudicious and prolonged use of a Thomas collar or other supportive devices contributes to the formation of fibrosis; I believe this type of support should be used only for a short time and that active movement should be restored as soon as possible to avoid fibrosis and disability.

Figure 3 shows a lateral roentgenogram of the cervical spine in what would be termed a normal individual, insofar as there has been no history of injury to the

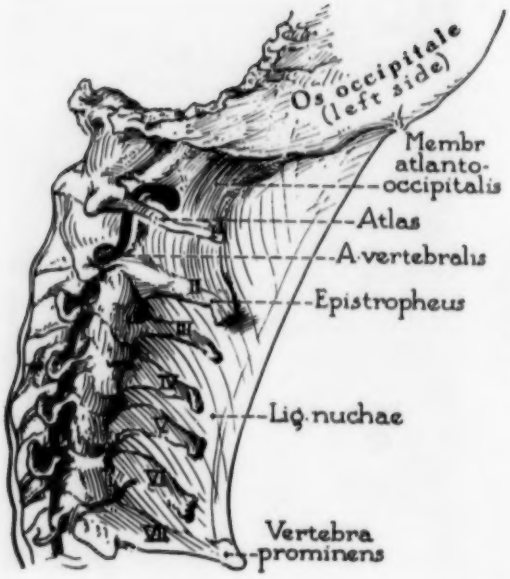


FIG. 2. A drawing of the cervical vertebrae showing the course of the vertebral arteries, the right and left both passing through the lateral portions of the cervical spine between the lamellae.

neck and no arthritic changes. Here again there are eight cervical vertebrae and some loss of the normal anterior curvature of the cervical spine. This is the usual type of picture seen in the so-called lateral erect roentgenogram of the cervical spine. The line of the facets, or articulating surfaces, and the line of the bodies of the vertebrae form parallel lines without offset interruption; this is in contrast to what would be seen in a dislocation or subluxation of any one of the vertebrae. It is in the diagnosis of injury to the facets, or the structures making up the joint bearing surfaces between these vertebrae, that controversy so often arises. Ordinarily, injury to the body of the vertebrae is more easily recognized and rarely raises points of dissension.

When it is necessary to show the first and second vertebral bodies, a roentgenogram such as the one in figure 4 may be used. It is taken with the mouth wide open to show in detail the articulating surface between the first and second cervical bodies and particularly to show the location of the odontoid process or "little spur" that runs upward from the second cervical vertebra and forms an anchor into the atlas. Avulsion or fracture in this odontoid process sometimes occurs in whiplash injuries and this type of roentgenogram will demonstrate the condition if it exists.

In figure 5 is shown the cervical spine in the anterior-posterior position, demonstrating the odontoid process rising and anchored by ligaments to the atlas. Also shown is the articulating surface between the atlas and the cranium itself. With these various fulcrums and articulating surfaces, almost any directional motion can occur at the junction of the atlas with the occipital bone of the skull; this is also true of the articulation surfaces between the upper cervical bodies. But, at the

FIG. 3. A lateral roentgenogram of the cervical spine in a person without a history of injury to the neck or arthritic changes.

odontoid process, any loss of the fulcrum and the anchor completely destroys the mechanism of motion at this point.

In the diagnosis of whiplash injuries, the technique illustrated in figure 6 is of special interest. Here the head is not only turned acutely to the right, but it is also brought down so that the soft tissues of the chin and the shoulder are in approximation. The subject is almost completely flat on his back so that there is minimal rotation of the trunk. The intervertebral facets are clearly shown, as are the articulating surfaces; on the left side of the neck, the spacing between each of the vertebrae has been increased so that roentgen-ray visualization for injury or abnormality is greatly enhanced. This procedure is based on what is called the Boylston technique and was, as far as I am aware, first introduced at an Academy of Orthopedics meeting and again at an American Fracture Association meeting in Houston. Let me empha-

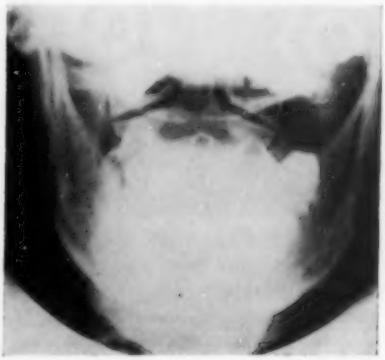

FIG. 4. A roentgenogram showing the first and second vertebral bodies.

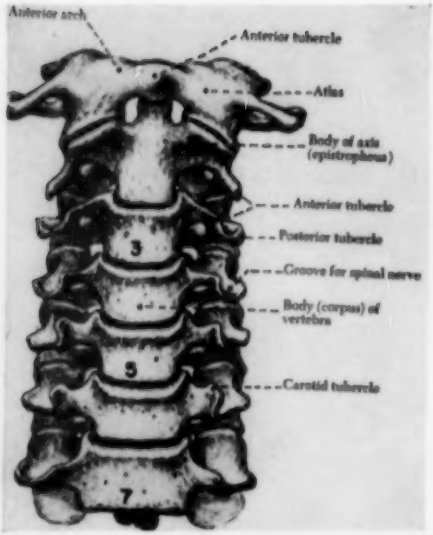


FIG. 5. The cervical spine in the anterior-posterior position is shown, demonstrating the odontoid process rising and anchored by ligaments to the atlas. Also shown is the articulating surface between the atlas and the cranium itself.

FIG. 6. Roentgenologic technique used for the diagnosis of whiplash injuries.

size that this is not "trick photography"; it is a valid attempt to visualize, by roentgenography, anatomic structures of the cervical spine. I believe that this particular procedure will become increasingly valuable in determining whiplash injuries, particularly when examining the bony structures of the neck.

# Ophthalmic Aspects of Whiplash Injuries

*J. Myron Middleton, M.D.*

The pupil of the eye and its associated structures can provide many valuable clues in diagnosing residual trauma from whiplash injuries. This becomes clear when we study the eye in relation to the nervous system pathways.

The pupil is dually controlled by the autonomic nervous system; the parasympathetic nervous system constricts it, while the sympathetic nervous system dilates it. In these primary ocular reflexes, the afferent path begins in the retina and ends in the Edinger-Westphal nucleus situated in the midbrain. The constrictor efferent fibers begin in the cells analogous to those in the lateral horn and then travel via the third nerve to the ciliary ganglion, and short ciliary nerves travel thence to the constrictor of the pupil. The dilator afferent pathway begins in the retina and travels through the optic nerve with a partial decussation in the chiasm, through some extra pyramidal tract to the midbrain, pons, medulla, and spinal cord, to the lateral horns from vertebrae C8 to T4, the so-called ciliospinal center of Budge, at which point there is a decussation, rendering possible the consensual reflex.

The efferent path of the dilator fibers consists of preganglionic fibers, anterior roots, white rami, and the cervical sympathetic chain of inferior, middle, and superior cervical ganglia. The final postganglionic fibers are transmitted to the eye via the carotid plexus and, from this plexus, three divisions reach the palpebral muscle of the upper lid, the orbital muscle of the lower lid, and the dilators of the pupil. The entire course of the pupillary constrictor elements is intracranial and thus relatively protected from cervical injury. But the sympathetic nervous system is in double jeopardy, since it traverses the cervical region twice, once as it descends to the ciliospinal center within the spinal cord and again as it ascends to form the carotid plexus. Except for superficial branches going to the external carotid artery, which are related to perspiration, it continues to be a deep structure from then on. Because of its vulnerable position in the cervical region, the sympathetic chain assumes the greater importance of the two systems.

The interruption or dysfunction of the sympathetic pathways to the head, which can occur in whiplash injuries to the cervical spine, may produce the well-known Horner syndrome, which has been described as a "sympathetic ophthalmoplegia." De Jong lists the etiologic factors of this syndrome in their order of frequency as follows: tumor of the spinal cord, syringomyelia at the level of the ciliospinal center, cervical rib, cervical tumor or enlarged lymph nodes. He also includes aortic aneurysm, tumor of the upper mediastinum, and diseases of the pulmonary apexes. Seen more rarely are radiculitis, diseases of the esophagus, and adenoma of the thyroid gland. Diseases of the thyroid gland are of special interest; another paper in this symposium (Morrow) mentions an acute episode of hyperthyroidism following whiplash injury. Further causes of Horner's syndrome are trauma of various kinds, e.g., bullet and stab wounds. Various hereditary factors have also

been reported, including unilateral pigmentary loss in the iris. It was at one time believed that the pupil had no dilator muscle because it could not be identified pathologically; but we now know that this muscle exists, although it is so heavily pigmented that the pigment must first be removed to establish its identity.

Injury to the descending pathway in the brain stem, medulla, and upper cervical cord can also cause Horner's syndrome. Further causes are fracture of the spine, the clavicle, and of the upper ribs, occurring in accidents, at birth, or late in life. It is of great interest that injury to the intracranial or protected portion of the carotid artery can produce the syndrome without ipsilateral, pseudomotor paralysis. The above lesions all represent an interruption of the sympathetic pathways. Bing has reported a spastic mydriasis resulting from a hematoma in the neck. Geiger reported a cervical migraine resulting from a head injury and subsequent osteochondritic changes. These were most frequently marked between vertebrae C3 and C8. A common precedent is said to be head injury involving degeneration of the intervertebral discs.

The ciliospinal reflex has long been known to produce mydriasis. The test consists of painful pinching of the side of the neck and observation of the pupil on the same side in a subdued light. The exact anatomy and physiology of the sympathetic nervous system is not known and its pattern is, moreover, not consistent in all species. There is not even a consistent anatomy in the same species, nor is there necessarily a symmetry of the sympathetic nervous chain on each side of the neck in a given individual. Patients with whiplash injuries frequently present vague visual complaints. It is sometimes difficult for them to describe these complaints. They say they have "blurred vision," or "objects seem to recede," or "I seem to lose my focus." Cogan has stated that sympathetic stimulation flattens the lens of the eye, anteroposteriorly, and accommodates the eye for distant objects. This is associated with dilatation of the pupils. Dilated pupils and a flattened lens are part and parcel of the same stimulation. In contrast, the parasympathetic system helps to focus closer objects. The effect of sympathetic paralysis, while usually not sufficient to make the patient obviously myopic, is nonetheless apparent with refraction. Changes in accommodation that are not completely subjective can thus be explained on the basis of sympathetic irritation or interruption.

The current emphasis on pupillary changes in whiplash injuries renews our detailed interest in the pupil as a valuable aid to diagnosis. Stern stresses the value of studying pupillary oscillations with the slit lamp. Perhaps, in the not too distant future, pupillography may become a common procedure in the office, as common as roentgenography is today. With a more refined technique, we will be less inclined to consider complaints as functional because we cannot satisfactorily prove them to be organic. When it is realized that, in addition to the legion of eye signs caused by head injuries, we have those resulting from whiplash injury, the ophthalmic evaluation of patients becomes very important.

# Whiplash Injuries to the Ear

*Lawrence K. Gundrum, M.D.*

A cursory examination of the medical literature on whiplash injury does not reveal any reference to otologic symptoms, either subjective or objective, with the exception of auricular or postauricular pain. My own observations on this lesion are limited to 5 cases, in spite of the large number of industrial accident cases of head injury that I have seen. This fact in itself suggests that whiplash cervical trauma rarely produces symptoms of otologic significance, with the exception of pain referred to the ear.

Possible sites of injury in whiplash accidents are best appreciated by recalling a few details of the anatomy and physiology of the ear. Figure 1 is a semidiagrammatic illustration of the sagittal section of the ear. The external ear consists of the auricle (A) and the external auditory meatus (B), which leads to the eardrum (C). The middle ear may be compared to a tiny box, the outside of which is the eardrum. In this box, there are the three ossicles: the incus, (D), malleus (E), and stapes (F). The malleus and the incus articulate with the eardrum and each bone is connected to the other by tiny ligaments. The stapes connects with the inner ear through the oval window (G). The internal auditory meatus (H), or eustachian tube, connects the middle ear with the nasopharynx.

The function of the auricle is to collect sound waves and transmit them through the external auditory meatus to the eardrum. The drum vibrates rapidly and amplifies sound in a manner that is similar to the action of the head of a bass drum. These waves are then transmitted through the ossicular chain to the inner ear. The inner ear is composed of two portions: the cochlea (J) and the semicircular canals, or vestibular apparatus (K). The cochlea resembles a snail shell; it is filled with fluid and lined with tiny hair cells, which are the end organs of the nerve of hearing. These cells are collected into a nerve that is the auditory portion of the eighth nerve (L). The vestibular portion of the inner ear consists of three tubules or canals, filled with fluid and lined with hair cells. These cells unite to form the vestibular portion (M) and, when united with the auditory portion, form the eighth cranial nerve (N), which travels to the midbrain. The vestibular apparatus controls the sensation of the body's position in space and its equilibrium.

Traumas may affect the ear by direct injury that destroys various parts of the ear, by long continued or sudden loud noises, or by concussion of the labyrinth or the brain. Bleeding in the ear may denote actual tearing of soft tissues or a skull fracture involving the temporal bone, which contains the middle and inner ear.

In determining whether a trauma to the ear has occurred in connection with an injury, the following data are pertinent:

1. Age and general health of patient. It is important to know the age of the patient because, after the age of 50, presbycusis (aging of the ear) may occur. It has been estimated that, after this age, hearing may degenerate at the rate of about 0.5 per cent per year without any other apparent cause. Acute diseases, such as mumps, whooping cough, measles, scarlet fever, and some general diseases, such as

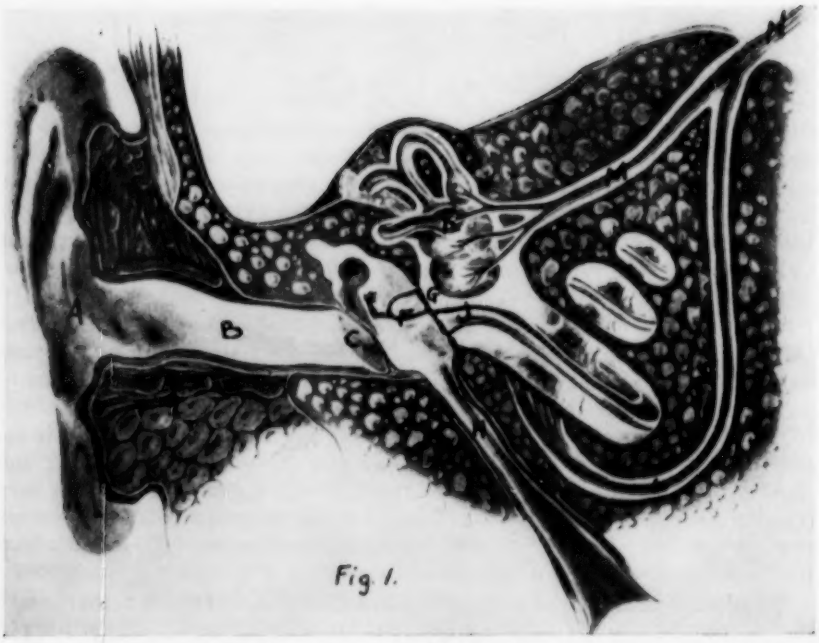


FIG. 1. Semidiagrammatic sagital section of the ear. (A) auricle, (B) external auditory meatus, (C) membrane tympani, (D) incus, (E) malleus, (F) stapes, (G) oval window, (H) internal auditory meatus, (J) cochlea, (K) vestibular apparatus, (L) auditory portion of eighth nerve, (M) vestibular portion of the eighth nerve, (N) eighth nerve.

syphilis, tuberculosis, and diabetes, sometimes have a deleterious effect on the ear. A few drugs, such as quinine, may also cause deafness.

2. History of the accident. To obtain a helpful history, one should ascertain the nature and time of the injury and the length of time after the accident when symptoms occurred.

3. Previous ear, nose, and throat condition. One must find out, if there was ear, nose, or throat trouble before the accident and, if so, its nature and extent.

4. The patient's complaints, especially of dizziness, loss of hearing, pain, tinnitus. Dizziness suggests a vestibular upset; tinnitus often accompanies deafness.

5. A careful ear, nose, and throat examination. This should include: inspection of the eardrum with a magnifying otoscope; inspection of the nasal secretions before and after shrinkage; transillumination of the sinuses; roentgenograms, if necessary; the use of the nasopharyngoscope; inspection of the throat and larynx; a microscopic study of the secretions of the nose and postnasal space, and determination of the patency of the eustachian tube.

6. Tests of hearing. These are done to ascertain if there actually is any hearing loss and, if so, the type of deafness that prevails. The hearing is tested with the

audiometer, a precision instrument that produces pure tones by electrical vibrations. It is also important to use calibrated speech testing through this instrument.

7. Various malingering tests. Many of these tests are done routinely to determine whether or not the patient is telling the truth. We are able to mask out all hearing in one ear while testing the other, if this is desired. If there is a great difference in hearing between the two ears, tones may be transmitted through the skull from the deaf ear and heard in the good one, thus giving a false picture of the true hearing in the deaf ear and also confusing the patient. It is best to test the hearing several times on different days to obtain an accurate diagnosis.

8. Test of the vestibular apparatus. These are of definite value in many cases to determine whether or not the inner ear has suffered trauma.

Deafness is generally divided into three types: conduction, nerve type (perceptive), and mixed. It is possible in some cases to determine whether the nerve type is in the cochlea, auditory nerve, or brain, but this test is not in universal use and is not completely accurate. Conduction deafness is caused by a lesion in the external ear, the middle ear, or the eustachian tube. In nerve type deafness, the lesion is in the cochlea, auditory nerve, or brain. In mixed deafness, the lesions may be in all parts of the ear. Usually, in the conduction type of deafness, the lower tones are more apt to be affected than the higher ones, and bone conduction is better than the air conduction. In the nerve type, the opposite is true.

Other means of making a diagnosis involve use of the audiometer. The test is for the phenomenon of recruitment, which is characteristic of nerve type deafness, in which the tones actually cause pain when they are a little louder than necessary. This is called the "threshold of discomfort." We also obtain the most comfortable listening level. This level is usually lower in proportion to the hearing in nerve type deafness than in conduction deafness. The audiometer records hearing loss in decibels. The Committee on Hearing of the American Medical Association has devised a method of converting decibel loss into percentage loss for the tones used in conversation or, in other words, the percentage loss of useful hearing. Figure 2 is an audiogram of a case typical of nerve type deafness following trauma; figure 3 is one of a case of conduction deafness; and figure 4 is one of mixed deafness.

Examination of the vestibular apparatus is begun by ascertaining the presence or absence of spontaneous nystagmus (involuntary movement of the eyeballs), which may be lateral, vertical, rotary, or mixed. Any spontaneous nystagmus is abnormal. The patient's position is suddenly changed, sometimes producing nystagmus, which also indicates a vestibular upset. The patient is turned 10 times in 20 seconds, which usually produces nystagmus in the normal individual. The ear is then irrigated with water and the reaction that follows depends on the temperature of the water, the duration of the irrigation, and somewhat on individual susceptibility. The normal response to douching with iced water is immediate nystagmus and often sweat, pallor, nausea, and, rarely, vomiting. However, if water at 68 F. is used, nystagmus occurs in 15 to 30 seconds, but sweat, pallor, nausea, and vomiting usually do not occur, unless the irrigation is continued for a longer period of two to five minutes. If the vestibular apparatus has been disturbed, irrigation with water at 68 F. produces exaggerated constitutional responses much sooner, often within 30

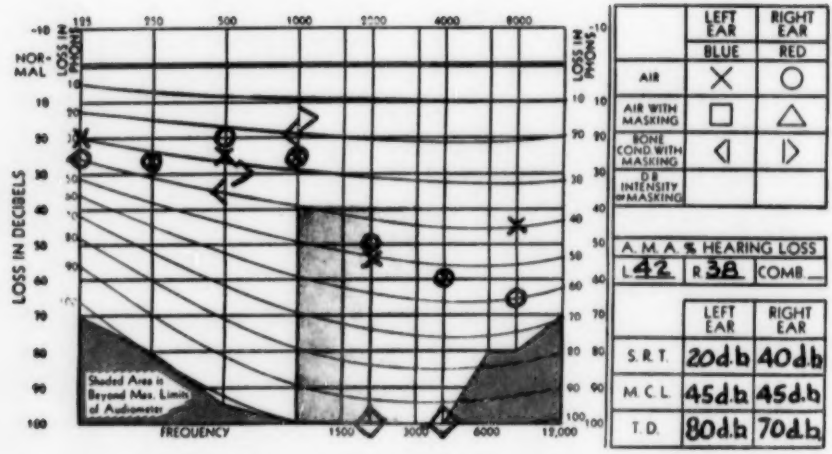


Fig. 2. Audiogram of a case of nerve type deafness.

seconds. This observation is important in suggesting trauma to this portion of the inner ear.

Of the 5 patients I have seen who had experienced whiplash injuries, 4 complained of pain in the region of the ear, 3 of tinnitus, 2 of loss of hearing, but none suffered dizziness. However, the pain was not related to the ear itself, but rather to the area immediately behind the ear. It may be that this postauricular pain is directly linked to injury of the postauricular nerve and not related to the ear per se. In

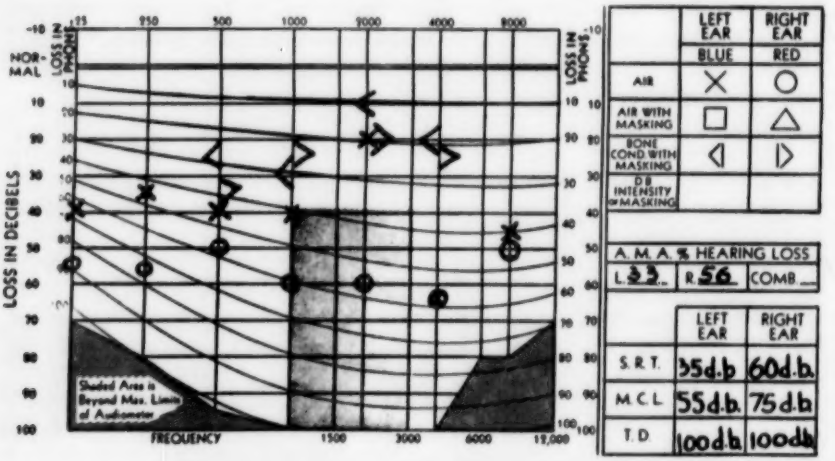


Fig. 3. Audiogram of a case of conduction deafness.

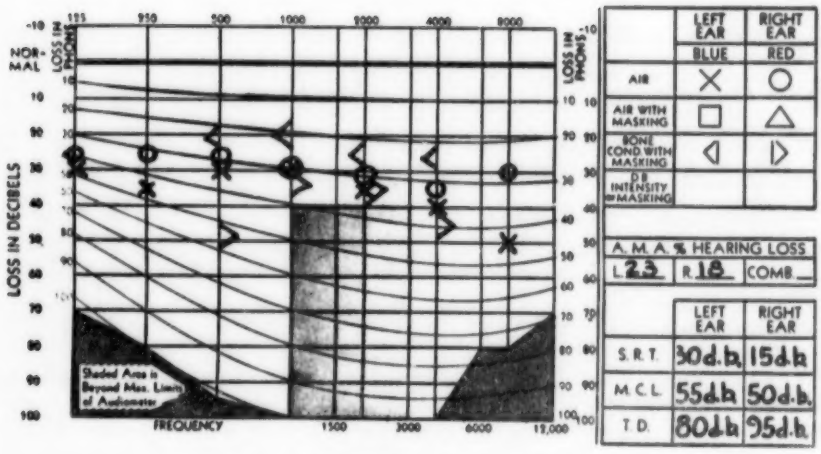


FIG. 4. Audiogram of a case of mixed deafness.

support of this theory is the fact that 2 of the 5 patients with whiplash injury complained of deafness. Hearing was found to be normal in 1 and the other had deafness that antedated the injury. Also, the latter was the only 1 of the 5 who exhibited exaggerated constitutional reactions to douching of the ears with water at 68 F. for 40 seconds. None of these patients had spontaneous or positional nystagmus: 3 complained of tinnitus, so that the possibility of involvement of the ear by whiplash injury cannot be entirely ignored, as far as these 5 patients were concerned.

In 100 cases of head injury I have observed, 57 patients exhibited exaggerated constitutional reactions to tests. Twelve others had spontaneous and/or positional nystagmus. All but 8 complained of dizziness and 50 also complained of deafness, pain, and tinnitus. Forty-five of the patients with these four symptoms or complaints were tested by irrigating the ears with water at 68 F. for 30 to 40 seconds: 26 exhibited hyperactive constitutional reactions; 13 reacted normally; and, in 6, the test caused little, if any, nystagmus. The latter were also tested by douching the ears with iced water and there was still very little response. Eighty-two patients complained of deafness, which was substantiated by auditory tests in all but 3; 74 had nerve type deafness and the other 5 had conduction deafness. No complaint of deafness was made by 21 patients, but tests of hearing revealed that 7 actually had some degree of nerve type deafness.

The exaggerated constitutional responses to douching the ears with water at 68 F. were not of significance in the 5 cases of whiplash injury that came to my attention, with the exception of the 1 case in which an old deafness had existed before the injury. It would seem, therefore, that this particular finding would not be significant in whiplash injury. But, if injury to the head occurred in connection with whiplash injury, the abnormal constitutional responses to douching the ears with water at 68 F. might be of value in suggesting that the inner ear was involved.

# Diagnosis of Whiplash Injuries

*J. Sloan Berryman, M.D.*

The complaint that occurs most often in whiplash injuries is headache. The pain ordinarily starts in the neck or over the shoulders and radiates along the back of the neck, almost invariably with a component of pain behind the eye, on one or both sides. There is some similarity between migraine headache and the whiplash type of headache, but the latter is not due to increased circulation in the head, as one can easily verify by compressing the internal carotid artery. In a person with true migraine, this would give immediate and prompt relief, whereas, in the patient with a neck injury, no relief is obtained by this maneuver. These patients ordinarily complain that inactivity brings on their headaches. Headaches are said to be worst before getting out of bed in the morning, though they are improved after moving about for five or ten minutes. The reason for that is probably the stagnation of circulation inherent in lying in bed, with compression on the tissues of the neck, by pillows and other structures, that interferes with venous drainage and produces some degree of passive congestion. This can be verified by prescribing nicotinic acid.

The patients with injury to the lower portion of the neck present a different set of complaints. They claim soreness in their shoulders—pain of a deep, boring, rather constant type that radiates down the upper extremities into the hands. Sometimes the zone of radiation is localized in the thumb and index finger, for instance, the distribution of the sixth cervical nerve, or in the little finger or the fourth and little finger, the distribution of the eighth cervical nerve. These patients have suffered some direct stretching and traumatizing injury to this particular component of the brachial plexus. These patients ordinarily do not suffer with many headaches and they usually can move their neck more freely; their complaints are confined to the upper extremities as a rule.

Examination of the patient in the office may reveal that the head is in an abnormal position and does not freely rotate from side to side. Observation should be made while the patients are sitting down; as one moves around the room in talking to them they are more or less obliged to turn the head. It should be noted that many of these patients come to the physician knowing that they are going to court and that the physician will be the expert who is going to testify about them in court. They must, therefore, attempt to impress their complaints on the physician. Ordinarily, up to that point, their complaints are not documented by neurologic findings. If the physician points out that he can find nothing wrong, the patient will magnify his complaints every time he goes to another physician. This is not malingering; these patients have an injury and its symptoms are real to them. The only thing they can try is to convince the physician that the pain exists; more anxiety thus builds up as patients continue to magnify their complaints.

Electromyographic tests have become very useful in this type of injury. When there is a crushing injury to a nerve but that nerve is still intact, the nerve impulse

may be so deranged as to produce a complex discharge resulting in multiple deflections above and below the baseline, instead of two or three. This indicates that the nerve is intact but the arrival of the nerve impulse is no longer brief and abrupt. It has become dispersed in time and produces a little less effective contraction. This is also seen when something happens to the blood supply of a nerve, though the nerve is still intact. In the whiplash type of neck injury, one does not as a rule see any evidence of complete destruction of the nerve with fibrillation.

In the treatment of these patients, pain relieving drugs are generally out of the question, unless they are very minor, such as aspirin or Anacin. I prefer to use vasodilating drugs, the most economical being nicotinic acid. Cervical traction and mechanical treatment of the neck are useful in many cases. It is preferable to have the patient take the equipment home with him and use it as often as necessary. This reduces the cost of treatment, since the device can be bought for the cost of two physiotherapy treatments. Additional treatment can be prescribed as required, depending on the use made of the traction device by the patient.

# Importance of Whiplash Injury

*John H. Schaefer, M.D.*

Some time ago, two neurologists published an article in the *Journal of the American Medical Association*,* in which they belittled the importance of whiplash injury. One of their conclusions was that 60 per cent of the victims of a whiplash injury eventually become neurotic. The apparent basis for that statement was the fact that they could find nothing in roentgenographic examination to justify the victims' complaints.

In a subsequent communication to the Journal, I criticized their concept of the manner in which whiplash injury is sustained, pointing out also that the absence of roentgenographic evidence of injury is absolutely no justification for stating that the patients did not experience a real injury. I emphasized that ligaments could be torn, hemorrhages produced, and that fibrosis could develop in injured muscles and in and around damaged nerves following hemorrhage.

In other papers in this Symposium, Dr. Morrow and Dr. Berryman have both pointed out that negative roentgenograms mean little, confirming the statements in my earlier communication. It should be emphasized that the cervical vertebrae are more delicate than the other vertebrae. Not only are they more delicate, but the cervical spine is far more mobile than other parts of the spine and it is less adequately supported.

From the pathologic standpoint, I encountered 2 or 3 cases before the war in which there were demonstrable fractures of the cervical vertebrae. My greatest experience, however, was during a period of eight years when I was one of the autopsy surgeons for the Coroner of Los Angeles County and thus frequently encountered the ultimate in whiplash injury. In probably 8 or 10 cases, there were complete dislocations of the skull upon the spine. In other words, the automobile in which the victim was riding had been hit from behind and the body and neck had simply been pushed out from under the skull. I have also performed autopsies on a number of persons who had fractures, with severance of the spinal cord, some of whom lived for a time after the accident. In that work, we usually had police photographs and reports on the accident to provide data on how the accident occurred. In my experience, a whiplash injury of the neck can range from transient sprain and pain in the neck to the ultimate fracture, with severance of the spinal cord. The material presented by other authors in this Symposium should help to refute the claim that 60 per cent of the victims of whiplash injury are psychoneurotic, a claim that I personally reject.

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* J. A. M. A. *152*:1698, Aug. 29, 1953.

# Dynamics of Car Crashes

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Some years ago, in the Engineering Department at the University of California at Los Angeles, we became interested in automobile crashes mainly from the standpoint of prevention. I had been in the business of accident prevention for many years before joining the staff of the University and had a strong interest in this matter. For many years, a great many efforts had been made in the field of accident prevention and we thoroughly agreed with those efforts.

We went into the field, with the cooperation of the Los Angeles Police Department, knowing the dynamics of the problem and believing that we might gain some new knowledge. We found out that we were wrong. One of the key problems was to determine the pre-impact velocity of a car. One can make calculations from skid marks to show the minimum speed, but this is a very crude method of approximation and does not supply the factors required later to calculate the forces to which a body is subjected in a collision. We undertook controlled experiments but found the problem just as difficult, if not more so.

We then moved into the field but under controlled conditions and not on public streets, so that, in effect, we had merely transferred the laboratory to a full-scale experiment. Cars were equipped with various instruments and contained mannequin dummies. High speed motion picture cameras were used to coordinate our data. We conducted a number of crashes and arrived at certain conclusions based on our measurements. We became acquainted with Lieutenant Colonel John Stapp, Medical Officer of the United States Air Force, who had conducted experiments on linear acceleration at Muroc. Some of his results are extremely valuable, since he has arrived at approximate figures on three points of vital importance in the type of collisions involving forward motion of the occupants of an automobile. The first is the G (Newtonian constant of gravitation) loading to which a person is subjected. The second is the rate of onset of the G loading, i.e., how quickly a peak or some high level is reached. The third is the length of time in which a person is subjected to the G loading. As we published some of our results, we were fortunate in attracting the attention of many members of the medical profession. Dr. Bechtol was one of several who were interested, and later Dr. Billig, thus giving us support from the medical profession. Through them we became interested in the so-called whiplash injury.

We then conducted some experiments in that field. The results have not yet all been analyzed, since it requires many weeks to read the high speed films. One experiment in rear-end collisions consisted of having a stationary car crashed into by a moving car. We first tried this at 7 miles per hour, with a dummy (mannequin) in the stationary car and a live driver in the colliding car, the power car. After observing the results, we put a live driver in both cars and again caused a collision.

The second test was performed at an approximate velocity of 11 miles per hour. Crashes with a dummy in the stationary car and a live driver in the second car were alternated with those having live subjects in both cars. These were done up to 20 miles per hour, at which speed we stopped.

On a previous occasion, we ran a test crash into a fixed barrier, a head-on type of collision, using a human subject at a very low speed. In this case, he wore a Navy aviator's type of helmet, on the back of which was an accelerometer weighing one pound. The head weighs about 12 pounds. There is a lever action involved, because the center of gravity in the head is some distance above the neck. At a speed of approximately 5 miles per hour, the subject felt that he was "not prepared to go any further." He felt a cracking sound somewhere in the vicinity of the cervical spine during the crash and suffered pain for some time afterward; although he did not become incapacitated, we realized that we were a little too close to danger.

With rear-end collisions, the deviations from the normal seating position that occurred were rather startling. The whole seat was pivoted at the bottom, the forces being so great at a 20 miles per hour collision that a permanent defect was forced into the metal of the seat. It takes a tremendous force to put a permanent kink into the frame structure.

We found, in the head-on collisions, that the frame of the car shows a much higher loading capacity than the body; the structural resistance to damage is many times greater in the frame than in the body. When we investigated accidents on the highways, we also noticed that, in most of the cars that seemed to be in extremely bad condition, horribly distorted, and wrecked (but not rolled over), the portion of the car behind the fire wall, the body part in which people ride, was almost invariably intact. Some parts might have been damaged, but the general contour was unchanged. That observation stimulated us to continue our research into the dynamics of vehicle collisions.

ARE THERE ANY "MINOR" ANTIBIOTICS? There are no minor drugs of any kind as long as they serve a clinically needed therapeutic function. In the book "Polymyxin, Neomycin, Bacitracin," Ernest Jawetz writes on three antibiotics which are only now coming to be recognized for their true usefulness. The specificity of polymyxin for Pseudomonas aeruginosa and of bacitracin for the staphylococci makes them of major importance to the clinician confronted with infection refractory to the more widely used antibiotics. Neomycin has found its greatest usefulness in topical preparations, although because of its wide antimicrobial activity it is now preferred in preoperative abdominal surgery.[1]

RHEUMATOID ARTHRITIS: CORTISONE OR ASPIRIN? There is little to choose between cortisone and aspirin in the management of patients in early stages of rheumatoid arthritis, according to the Joint Committee of the Medical Research Council and Nuffield Foundation. Their conclusion is based on a two-year study of 61 patients, 30 of whom were treated with cortisone and 31 with aspirin.[2]

NEW VENOUS SHUNT. A new side-to-end type of portal-to-systemic venous shunt has been designed primarily for patients in whom the splenic and portal vein sites are unavailable for decompressive procedures. This technique is also successful in children.[3]

CHLORPROMAZINE FOR MENTALLY RETARDED. A "phenomenal" rise in the I.Q. is reported in a group of 10 hyperactive, mentally retarded children given chlorpromazine in three daily doses of 25 mg. orally for 60 days. An average increase in I.Q. of 10.4 points per child occurred at the end of two months. The rise in the control group was only 2.5 points. The children were quieted down and slept better.[4]

SULFONAMIDE OR INSULIN? According to three reports from Germany, a simple sulfonamide, orally administered, could replace insulin control of diabetes mellitus. After gradual withdrawal of insulin, patients can be maintained on one tablet daily of BZ 55 ($N_1$-sulfanilyl-$N_2$-n-butycarbamide). Rapid depression of blood sugar levels has been noted following the administration of 4 Gm. of BA 55 in divided

doses. Thereafter, 1.0 Gm. per day maintains effective control of diabetic patients. Neither toxicity nor side effects were seen.[5]

NEW PROGRAM FOR WOMEN PHYSICIANS. The first international educational program for qualified foreign women physicians will be launched by the New England Hospital early this year (1956). Applicants require a basic working knowledge of English. The program includes a month's indoctrination of English, medical terminology, techniques and a one-year rotating internship with courses in the basic sciences as well as current medical advances. Ten scholarships totaling $5000 will be offered.[6]

RECOMMENDATIONS FOR THE AGED. Long-term anticoagulant therapy for patients who have had myocardial infarction is advocated by Nichol (Miami Heart Institute).[7]

A 3-way stopcock should be used on an infusion set when infusions or transfusions are necessary, suggests Deitrick (Jefferson Med. Coll., Phila.).[8] Venous pressure should be measured continually; if it rises, the amount and speed of transfusion can be reduced. The author feels this is of great importance in the elderly, especially pre- and post-operatively.

Protection from infection is strongly urged by Long (N.Y. Coll. Med., Brooklyn).[9] Prophylaxis with broad-spectrum antibiotics prevents minor infections and reduces hospital stay. The author employs tetracycline, 0.5 Gm. daily in divided doses. Only one patient in 500 showed symptoms of diarrhea.

Avoid barbiturates and bromides for sedation at night, counsels Wortis (N.Y.U.),[10] who prefers giving whiskey or chloral hydrate or both.

CHLORPROMAZINE FOR CHILDREN. Uniformly good results have been reported with chlorpromazine in the treatment of nausea and vomiting in children. The dosage used was 3 or 4 teaspoons daily, or by suppository, 25 mg. for children under six years, 50 mg. for older children.[11]


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## The Whip and The Man

The Symposium on Whiplash Injuries (pages 1–30) points up the regrettable oversight that while modern automobiles have increased enormously in power in recent years, nature has done nothing to increase the strength of man's cervical spine. The result is that when a 200 horsepower vehicle encounters an immovable object, or is thunderously struck from behind by another modified tank, the seven or eight vertebrae that compose the neck are lamentably mishandled. Dr. Billig and his colleagues give us a thorough if frightening description of the forces at work in a whiplash injury: compression, shearing, bending, distension, torsion, and, not infrequently, irreparable fracture. Some of these can be diagnosed by roentgenograms but as Dr. Fields points out, this is not always conclusive evidence of the injury done. The intricate cervical nerves may be involved, resulting in vasomotor disturbances long after the accident, for which he proposes the sensible term of "autonomic nervous system concussion." This point is also made in another context by Dr. Schaefer, whose experience with autopsy material has caused him to view roentgenograms with some scepticism. His scepticism is also applied to those who minimize whiplash injuries, claiming that a great many sufferers are merely neurotics.

We are reminded by Dr. Morehouse's excellent physiologic description that a neck injury may not be as simple as it looks, and that disturbances of the many finely balanced reflexes in this region can thoroughly upset the total body posture. This point is emphasized by Dr. Morrow's delineation of the anatomic structures involved in a whiplash injury, his "refreshers" in anatomy providing a precious help in diagnosis. The eyes and ears can also be valuable diagnostic aids. Dr. Middleton informs us that an examination of the eyes can often produce a clue to residual trauma, while Dr. Gundrum describes practical tests in diagnosis, particularly when the whiplash injury is associated (as it so often is) with a crack on the head. Further practical hints in diagnosis are given by Dr. Berryman, who describes some simple tricks to smoke out the malingerer angling for large legal damages. And finally, but by no means leastly, we have a description by Mr. Mathewson, an engineer, of tests that have been done with dummies and live "victims" to determine the dynamics of automobile crashes. Automobile manufacturers are becoming increasingly aware of the dangers to the human body in their chromium-plated juggernauts and are installing various tentative safety devices. This is all to the good, and this Symposium should stimulate them to still further efforts.

# Words and Images in Medical Communication

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The greatest problem of modern medicine is that of communication. Communication not only between the physician and the sick person, so indispensable particularly in psychiatry, but also between the investigator and his problems, the clinician and the patient, and the educator and his pupils. Especially vital is the need to communicate scientific finding, clinical data, medical discoveries, or the great-in-its-humbleness daily medical experience to the professional who needs to know all this in order to fulfill better his ministry. Despite the progress in radio, films, and television, books and journals are still the best vehicles of medical communication.

"There are only three pleasures in life pure and lasting and all derived from inanimate things—books, pictures and the face of nature," said William Hazlitt. These three supreme components are represented in a medical journal by the word, the image, and the phenomena of human nature either when it is normal or when it is undergoing that painful "mode of life" that we call disease.

"In the beginning was the Word . . ." and in the beginning as well as in the end the written word and the image were and will be the most faithful messenger of medical thought, a flowing tunic clothing thought without disguising its true form.

In the world of medicine, events occur in the hospital ward, in the physician's office, or in the research laboratory. After these phenomena have been recorded by the eyes and ears of the observers or by the camera's magic pupil, they are transmuted into words and images that later, on the printing presses, are converted through electrical impulses and mechanical vibrations into articles and photographs which, lastly, are integrated into the pages of a medical journal. As happens in every biologic cycle, this process is a continuing one. Readers of medical journals transmute in their minds the words and images into ideas and concepts that will help them in carrying on their research, clinical practice, or medical teaching, thus creating new links in this endless chain of development.

Medical journals integrate the three categories established by Osler—"creators, transmuters and transmitters"—since they create a climate of opinion around scientific problems, transmute phenomena and events into ideas and concepts, and transmit to their readers not only the golden stream of classical medical wisdom, but also that other "small" daily clinical wisdom which, like a fine rain of gold dust, is daily precipitated upon the mind of the general practitioner.

Like every living organism, a medical journal in the course of growth makes its internal structure more complex and its external appearance more definite. After this, it tends to enlarge its intellectual horizon—just as this journal has done in publishing its many symposia—and also to "dress up" in new clothing and ornaments

in order to underline the increased value of its contents through a more attractive outward appearance.

With this issue, the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS changes its external appearance, adopting a new color scheme and typographical style. We hope that these changes will symbolize a growing clarity and order in its contents so that the reader may climb to the new planes of conceptual architecture to which Medicine in our time is being raised.

One of the objects of this new conceptual architecture is to provide the gems of scientific progress with a setting of medical humanism, that humanism which, like an underground river, has watered throughout history the efflorescent discoveries of each period.

The new INTERNATIONAL RECORD OF MEDICINE cover is green and white—green like the Mediterranean olive groves that shaded the meditations of the fathers of classical medicine; white like the marble of the medical temples of ancient Greece around whose ruins are still knotted the roots of the golden-graped vines.

Superimposed on this olive-green and marble-white of our new cover are two seals symbolizing 119 years of American medical history, a long chain on which, like the pearls on a necklace, are threaded the contributions of the INTERNATIONAL RECORD OF MEDICINE to the progress of medicine.

Leonardo da Vinci once called for "the mellow voice of the lute and a picture that is crisp and bold." Heeding this call, the INTERNATIONAL RECORD OF MEDICINE will strive as in the past to offer its readers the same clear voice and bright picture that from its very beginning have made of it a quiet, orderly, and brightly lighted chamber in which have congregated all those who look at modern medicine with the same love of truth and awe of nature with which it was first regarded over four centuries ago by a physician named Vesalius. It is with these very same eyes that the medicine of the future will be regarded by the good physician of the next half-century.

*The readers of the journals of MD Publications, as well as of the books and monographs on antibiotics published by Medical Encyclopedia, may be interested to learn of the honor recently conferred upon the editors of these journals and of the* Antibiotics Monographs *series by the* New England Journal of Medicine, *the oldest medical journal in the United States.*

*In an editorial entitled "Antibiotic Monographs," published in the November 17, 1955, issue of the* New England Journal of Medicine, *the editorial scope and the scientific spectrum of these publications were generously commended. As a service to our readers, we are reprinting the editorial from the* New England Journal of Medicine *through the courtesy and kind permission of its editor, Dr. Joseph Garland.*

## Antibiotic Monographs*

During the past few years several thousand papers have been published each year, and an imposing number of books have appeared concerning antimicrobial therapy, the more recent ones dealing mostly with antibiotics. These papers and books have either presented or attempted to correlate the large mass of information that has accumulated so rapidly in this important area of medicine—important equally to the medical profession and to the great pharmaceutical and chemical industry. Some of the books have dealt with the general field; others have dealt with individual antibiotics or groups of chemotherapeutic agents, and still others have given attention to more basic problems involving the mechanisms of their action.

In this country Dr. Henry Welch, director of the Antibiotics Division of the Food and Drug Administration (now under the Department of Health, Education and Welfare), has taken the lead in an attempt to collect and organize the available information in this field. First he sponsored and organized antibiotic conferences, at which workers in industrial and in noncommercial laboratories, as well as clinicians and clinical investigators, could present and discuss all aspects of problems in this field. Then, with the co-operation of Dr. Félix Martí-Ibáñez, he sponsored and edited the special journal, *Antibiotics and Chemotherapy*, and its more recent clinical counterpart, *Antibiotic Medicine*. Together, they have also reinstated the antibiotic conferences on an annual basis and are publishing the papers presented at these conferences in volumes that, judging from the first two that have already appeared under the titles *Antibiotics Annual, 1953-1954* and *1954-1955*, seem to be of rapidly increasing size. With Dr. Charles H. Lewis, Dr. Welch also presented a comprehensive volume, *Antibiotic Therapy*, which he later edited in a revised edition as *Principles and Practice of Antibiotic Therapy;* the latter contains authoritative summaries of the available information about the more important and widely available antibiotics and their uses in the management of various groups of the common infectious diseases. A small volume, *The Manual of Antibiotics, 1954-1955*, contains a compendium of the preparations, a therapeutic index, lists of the generic and trade names and of the producers of various antibiotic preparations.

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* Reprinted from The New Eng. J. Med. 253:883 (Nov. 17) 1955.

*Antibiotic Monographs* is the most recent series of publications being undertaken under the editorial direction of Drs. Welch and Martí-Ibáñez and published by Medical Encyclopedia, Incorporated, of New York, which is also the publisher of the other journals and volumes mentioned. This new series is designed to present more complete and comprehensive monographs on either individual antibiotics or general topics. Two of these monographs have already appeared. The first one, *Erythromycin*, is by Dr. Wallace E. Herrell, a recognized authority on antibiotics who, with his former colleagues at the Mayo Clinic, carried out some of the early studies on the clinical uses of penicillin and subsequently contributed to the understanding of each of the successive antibiotics as they appeared. It will be recalled that Dr. Herrell, in 1945, presented one of the first comprehensive and practical books in this field, *Penicillin and Other Antibiotic Agents*. The monograph on *Erythromycin* gives, in 56 pages, a concise summary of the properties, pharmacology and practical applications of this agent.

The second monograph, recently released, is *Assay Methods of Antibiotics· A laboratory manual*. This one is by Dr. Donald C. Grove and Dr. William A. Randall, both of the Division of Antibiotics of the Food and Drug Administration, who are themselves responsible for many of the developments as well as the practical applications of these assay methods and are the authorities best qualified to cover this subject. This volume of 238 pages should serve as the source book for all laboratory workers who are confronted with the problem of assaying antibiotics.

*Tetracycline* is the title of Antibiotic Monograph Number 3 and is now ready for release; it is by Dr. Harry F. Dowling, professor of medicine and head of the Department of Medicine at the University of Illinois. Dr. Dowling is the author of the popular volume, *The Acute Bacterial Diseases: Their diagnosis and treatment*. He and his associates have made numerous valuable contributions to the clinical literature on antimicrobial therapy.

Monograph Number 4, entitled *Antibiotics in Nutrition*, which appeared early in October, is by Dr. Thomas H. Jukes, who, with his colleagues at the Lederle Laboratories and the Research Division of the American Cyanamid Company, pioneered the development of antibiotics as feed supplements to serve as growth-enhancing agents in animals raised for market. This volume presents a comprehensive review of the effects of antibiotics on the nutrition of animals and man and of the possible mechanisms by which this effect is accomplished. It should be of great interest to all those interested in nutrition, antibiotics and general biology, as well as in agriculture. Other important monographs by equally competent authorities on other topics of interest to practitioners and laboratory workers as well as to those in agriculture are planned.

Drs. Welch and Martí-Ibáñez are to be congratulated on their tireless efforts to present to the medical, pharmaceutical and scientific communities these very important and timely publications in an important field that now involves both human and veterinary medicine, as well as agriculture, general biology and organic, industrial and biologic chemistry.

# Food and Drug Administration Anniversary Editorials

In June of 1956, the Food and Drug Administration will have completed fifty years of service to this nation. In order to pay tribute to the outstanding achievements of the FDA, ANTIBIOTICS & CHEMOTHERAPY, ANTIBIOTIC MEDICINE, and the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS, journals of MD Publications, Inc., will publish a series of exclusive Editorials written by members and associates of the Food and Drug Administration on the various activities and different facets of the technical work that is carried on.

At the dawn of our century, in 1906, the Bureau of Chemistry, Department of Agriculture of the U. S. Government, was given the task of enforcing the Food and Drugs Act of that year as a protection to the nation's consumers. In 1927, the Food, Drug, and Insecticide Administration was established as a separate unit in the Department of Agriculture to conduct the regulatory work, including the necessary research for most effective enforcement. Three years later, the name of that organization was changed to Food and Drug Administration. In 1940, the Administration was moved from the Department of Agriculture to the Federal Security Agency, which in 1953 became the Department of Health, Education, and Welfare.

The evolution of the laws that have been enacted and the problems of enforcement are explained in these Editorials, which will present a majestic panorama of the endeavors and achievements of an organization dedicated to the noble task of cooperating with physicians, investigators, and other technicians in protecting the nation's health. The first of these Editorials will be found below and on the following pages.

## Stilbestrol as a Possible Food Additive

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Interest in the use of diethylstilbestrol as an additive to feeds for steers to produce an increase in rate of growth and an increase in the efficiency of utilization of food has grown very rapidly. In the last two years its use has become quite general. It has been reported that the increased rate of growth in steers fed stilbestrol at the rate of 10 mg. per day is approximately 20 per cent, and, concomitantly, there is a decrease of about 17 per cent in food intake per pound gain. The economic advantage of the use of diethylstilbestrol in feeding steers in feed lots is generally recognized.

The mechanism by which this change takes place is not clear. There is some evidence that stilbestrol, whether it be fed or whether it be administered in the form of pellet implants, increases the nitrogen retention. There is also evidence that this treatment produces a hypertrophy of the liver, the adrenal glands, and the pituitary without any specific cellular changes. These observations seem to indicate that there is a change in the endocrine gland metabolism, but exactly how these changes produce the increased growth rate and the increased efficiency of food utilization has not been clearly stated.

The Food and Drug Administration recognized the trend when it published on December 4, 1948, in the *Federal Register*, the general policy that in considering new drug applications for products intended to affect physiologic changes in farm animals, it would regard the absence of satisfactory evidence showing that the meat or other food obtained from animals fed such a drug is entirely free of any poisonous, deleterious ingredient resulting therefrom at the time of marketing as grounds for refusal to make the application effective. In line with this policy, prior to the general distribution of any stilbestrol-containing feed supplements, the Food and Drug Administration has required manufacturers to submit extensive evidence showing that there was no added estrogen in the edible part of steers fed diethylstilbestrol. Several companies have developed assay techniques the sensitivities of which are quite astonishing. It has been shown that meat from steers fed 10 mg. of stilbestrol per day when ready for market contains less than 2 parts per billion of added stilbestrol. Therefore it may be stated with considerable confidence that stilbestrol fed to steers under the conditions outlined by the manufacturers of feed supplements will constitute no hazard as an additive to food products derived from animals thus fed.

As a side issue to the general use of stilbestrol additives for steers, another problem relating to the occurrence of stilbestrol as a contaminant in feeds not intended for steers has arisen. On several occasions, feeds prepared for small laboratory animals have been run through mixers immediately following feeds prepared with stilbestrol for steers. The result has been an accidental contamination of the small animal feeds with stilbestrol. This contamination in some cases had quite serious effects upon the reproductive capacity of small animal colonies. The exact method of controlling such contamination and preventing its occurrence is under study by the Food and Drug Administration at the present time. It is hoped that methods of clearing mixing channels in food-mixing plants can be developed that will entirely prevent this unjustifiable and hazardous occurrence.

## The Skin Game

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Modern chemistry and technology are responsible for a rapidly expanding group of synthetic products. Many such new synthetic products have been proposed

for use or are actually used in cosmetics and topical medicines. In our modern industrial world, not only the plant worker engaged in the manufacturing and handling of these synthetic chemicals, but also to a lesser extent, the average individual regardless of occupation may be exposed to a wide variety of new chemical substances that have been introduced in his daily living. The need has arisen for the proper appraisal of the health hazards involved in the cutaneous and mucous membrane exposure to these products. Adequate appraisal of such hazards poses many problems in skin pharmacology and toxicology.

The Division of Pharmacology of the Food and Drug Administration is often called upon to review dermal and mucous membrane toxicity data, and to pass on the adequacy of such data, in support of evidence to demonstrate safety for use of a product. In addition, the division frequently finds it necessary to obtain its own toxicity data to permit decisions on products which may be in violation of the provisions of the Federal Food, Drug, and Cosmetic Act.

The skin is a large and important organ of the body. No other organ is exposed to as many or as varied external (often detrimental) influences, namely, wide fluctuations in external temperatures and humidity, and such other physical factors as chemical irritants, bacteria, virus agents, and any other offending material that may be present in man's environment. An important physiologic function of the skin is its role in serving as protective armor for the deeper tissues against trauma and desiccation. In addition, the intact skin also serves as a relatively effective barrier to the inward transfer or penetration of many substances. Paradoxically, the skin has been found permeable in some degree to a wide variety of substances. This is significant not only in cosmetics and topical medicine, but it also may assume, from toxicologic implications, some importance in forensic medicine.

Although the skin must be regarded as an entity comprising the epidermis, derma, and subcutis, problems in absorption are confined chiefly to considerations of the epidermal layers. Substances that have reached the derma with its extreme vascularity, readily enter the general circulation. The epidermis with its many imperfections or "breaks" in its architecture (as represented by the skin appendages: the sebaceous and sweat glands and their ducts, and the hair follicles) presents a sievelike structure capable of engulfing considerable material which in a physiologic sense has neither penetrated nor been absorbed. It is characteristic of warm-blooded animals that the outer cell layers of skin desquamate constantly and uninterruptedly. This gradual desquamation of outer cells of the horny layer illustrates a primary function of mammalian skin, namely, a characteristic designed to prevent the inward movement of materials that may come in contact with the skin. The process of cornification in the epidermis, that is, the formation of keratins, which are refractory chemical substances, is further evidence that the epidermis is a tough inert barrier to the percutaneous inward transfer of materials. Mammalian skin in its physical and physiologic behavior illustrates the principle that a most important function of this organ is to exclude, slough, and expel materials rather than to abet their penetration and absorption.

For obvious reasons, man is not the feasible experimental subject to use in the

acquisition of the bulk of the data in the determination of dermal or mucous membrane toxicity. Reliance for the evaluation of the toxicity of substances must be placed on laboratory animals.

Procedures to evaluate the toxicity of substances applied topically to skin and mucous membranes are numerous and involved. The various techniques are designed to estimate local effects (local toxicity) as well as systemic effects (systemic toxicity). The local effects are more properly termed "irritations," a general term to describe essentially contact dermatoses or inflammation of mucous membranes. Skin irritation may result from contact with substances that are primary irritants or from contact with substances producing sensitizations. A third type of skin irritation is now recognized which, for the lack of a better term, has been named "skin fatigue." Appraisal of systemic toxicity is made following dermal applications by acute (single) and subacute (multiple) exposures to the test substance. Exposures are made to the intact as well as the damaged skin. Data should include observations on symptomology, chemical studies, hematology, pathology, and physiologic function tests on treated subjects. Great significance is attached to a careful histopathologic examination of tissues of animals following treatment in the longer periods of multiple exposures.

It is not uncommon in studying compounds by the various dermal techniques to observe in some instances but slight effects on acute (single) exposure. However, the same compound may be found severely damaging when studied by subacute (multiple) exposures. The skin damage may range from a mild dermatitis to complete necrosis or severe eschar formation with desquamation. In such instances, the regenerating skin, as a rule, is more resistant to future action of the compound.

Adequate methods are available today to study the local and systemic toxicity of substances applied topically to skin and mucous membranes, and to permit an appraisal or evaluation of the extent of injury produced in these structures. Such procedures yield information on prognosis for repair and recovery. Analysis and assessment of data, a consideration of species differences, and the allowance for a margin of safety make possible an estimation, in the case of a given compound, of the amounts, concentration, and frequency of application that may be tolerated by man.

## Side Effects of Drugs

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Alexander, in his book entitled *Reactions with Drug Therapy*, has defined drug hypersensitivity as that which "connotes mechanisms that are responsible for lesions which differ from pharmacological effects of those of overdosage, and which are induced by therapeutic or subtherapeutic amounts." In addition, there are equally ardent advocates of the theory that such sensitivity is dependent on the

size of dosage, that response increases uniformly with the dose. Many instances of so-called sensitivity can be explained on this basis.

However, we would like to indulge in an expansion of the term "side effects of drugs" to include not only those reactions that may result from hypersensitivity, the latter said to be due to an allergic mechanism, but also to those effects that may simply result from an inadequate testing program. Such reactions may, therefore, include those expected from a toxic level of the drug. Animal toxicity studies can be designed to protect both the normally susceptible and the hypersensitive groups. This is accomplished for the normally sensitive group by requiring that there be an adequate margin of safety, and for the hypersensitive groups by appropriate tests for allergic manifestations by administration of the drug to animals peculiarly suited to such tests.

Margin of safety may be defined as the ratio of the therapeutic dose of a drug to the level that will just cause untoward effects. If this ratio is sufficiently high, then the hazards of administering that drug to the general public will be greatly diminished.

Testing procedures for the determination of the adequacy of drugs from a safety standpoint include not only the aforementioned toxicity studies, but also a standardization of the potency of the drug by chemical or biologic means, as well as rigid tests to insure proper hydrogen ion concentration, and sterility, where such tests are pertinent.

To go back a number of years, this complaint of inadequate testing, which has been long-standing, was brought into sharper focus by the unfortunate deaths that occurred as a result of the use of the "elixir sulfanilimide" in drug therapy. The responsible toxic agent contained in the drug preparation was the solvent, diethylene glycol. This incident occurred in 1937, and further pointed up the need for the "New Drug" provisions contained in the Food, Drug, and Cosmetic Act, which was passed one year later. Under these provisions, before a new drug can be distributed in interstate commerce, evidence of the safety of the article for the purposes intended must be submitted to the Food and Drug Administration in the form of a new drug application. However, despite the scope of the drug act, there remain instances in which more thorough testing of a drug or a druglike product would have prevented unfortunate incidents. In particular, reference is made to the salt substitute episode in which lithium chloride was offered for sale as a replacement for sodium chloride in those individuals who, as a result of heart conditions, could not tolerate the retention of fluids induced by diets of normal sodium chloride content. As a result of reports of toxic effects in persons using this product, lithium chloride was fed to laboratory animals. Deaths occurred at levels that did not provide a sufficient margin of safety. Further, the toxicity was accentuated when lithium was given to animals maintained on diets greatly restricted as to their sodium chloride content. Suffice it to say that the adverse effects noted in people using this product might have been prevented had a more adequate testing program been conducted.

The following are additional examples of complaints of injury that have led to the implication of various drug products. The drugs found to be at fault were

(1) a local anesthetic solution with excessive hydrogen ion concentration which resulted in death of tissues at the site of injection; (2) a veterinary salt solution which caused untoward effects and deaths in animals to which it was given intravenously. These effects resulted from failure of the label to bear adequate warnings that the drug should not be given too rapidly. A simple animal test would have prevented this. (3) Drugs for injection containing injurious quantities of surface active agents. These resulted in local damage at the injection sites. Many more such situations can be enumerated, but these suffice to impress one with the necessity not only for full investigations of a drug before it is put on the market, but also for careful control procedures as long as its production is continued.

Finally, an important consideration in the therapeutic field is that of synergism of drugs where only simple additive effects are anticipated. Often drugs, which of themselves are wholly satisfactory, will, when combined, eventuate in an extremely dangerous drug combination. It is for this reason that new combinations of old drugs are also required to have their safety established in a new drug application before they are marketed.

## Nerve Poisons

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A few years ago the mention of the term "nerve poison" was enough to raise the eyebrow of even the most conservative scientist as well as the uninformed layman. The term literally commanded respect, but, as with so many phrases in our language, it has lost its impact and instills little more emotion than an amber light at a traffic intersection. This deflation process has been catalyzed by articles in popular lay magazines and the widespread use of these materials as insecticides. Unfortunately, the compounds themselves have not lost their toxicity.

During the war years, the German government devoted vast expenditures of money to the development of these compounds as potential antipersonnel agents. Many of the compounds synthesized are among the most lethal chemicals ever discovered. Published reports show lethal doses as low as 20 μg./Kg. for rats. In view of the indications that man is many times more sensitive than the rodent, they should be reasonably good antipersonnel agents.

Shortly after the war, these poisons logically found their way into European and American industry as insecticides. Years of screening have separated a series of compounds that can be safely manufactured and are effective insecticides. Their lethal dose in rodents ranges upward from 1 mg./Kg., but their mechanism of action remains the same—inhibition of the enzyme cholinesterase. Without this enzyme, an accumulation of the chemical mediator acetyl choline occurs, causing convulsions, respiratory arrest, and death.

Many deaths resulted from accidental poisoning during the first few years that

these compounds were released for insecticidal use, but with experience the manufacturers and physicians learned to save a large percentage of these accidentally poisoned individuals through the proper use of atropine.

But this was only part of the fear of the Food and Drug Administration. This new insecticidal use engendered the contamination of food with all of its long-range implications. Could these compounds be used as insecticides without inflicting any additional biologic stress on the unsuspecting consumer? To answer this question, the Food and Drug Administration and the manufacturers conducted two year feeding studies in laboratory animals. Throughout the experiments the animals appeared normal, and at autopsy gross and microscopic tissue changes were absent. Mortality occurred only when the daily dosage approached the single lethal dose. It was difficult to avoid a conclusion that these compounds were not cumulative poisons. In 1950, this was almost a universal opinion, and the fear of continuous ingestion of small quantities was waning.

However, just as death is a very crude end point, so pathologic changes are an incomplete end point. For this reason, the Food and Drug Administration continued its investigations by searching out the enzyme changes that might reveal cumulative toxicity at small dosages. Here the changes were dramatic. As little as 0.1 parts per million in the diet or 1/1000 of the single lethal dose with some compounds could produce significant inhibition of the cholinesterase enzyme.

Thus, every insecticide currently used has been screened by the Food and Drug Administration or by the manufacturer for these effects. Several have been found to be too toxic for insecticidal use, while others have been permitted where the residue remaining at harvest is sufficiently below the level that might cause such enzyme inhibition.

The "nerve poisons" have found a useful place in the agricultural industry. However, our familiarity with them over the years should not have bred contempt, but rather even greater respect. They are not only acute poisons, but cumulative ones as well. Therefore, to maintain our food supply free from deleterious levels of poisonous chemicals, it is necessary to demonstrate the type and degree of cumulative toxicity. It is the responsibility of the Food and Drug Administration to see that safety is adequately demonstrated before general use is undertaken, and this responsibility is not taken lightly.

## Dermal Sensitization

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Several forms of allergic manifestations are known and distinctly recognizable. They are categorized as (1) anaphylactic, (2) bacterial or tuberculin, and (3) dermal, cutaneous, or eczematous sensitizations. The third category is of particular interest to the Skin Toxicity Branch of the Food and Drug Administration.

Problems involving dermal sensitization have become of paramount importance,

particularly within recent years, owing to the increased use of synthetic agents for cosmetic and detergent purposes. Irritation of the skin following the topical application of a cosmetic, or contact with a detergent, can occur in one of two forms. The response could be one of primary irritation, and if so, the causative agent is referred to as a primary irritant. While its mechanism of action is not fully understood, it is related, at least in part, to the inherent nature of the substance, its concentration, and the duration of exposure. In such cases, skin eruption is confined to the site of contact or application of the offending agent. In contrast to this, the skin can be exposed one or more times to a particular compound without the occurrence of an untoward response. However, with repeated or frequent exposure, as would result from the use of a cosmetic or detergent, a skin reaction may be elicited although the concentration of the compound is low and the exposure time short. Such a phenomenon is thought of as having been acquired, or the individual sensitized, and the condition is diagnosed as eczematous or contact dermatitis. Should the skin react in similar fashion following frequent short periods of exposure to a known primary irritant present in low concentration, the irritant is considered to be also a sensitizer.

Since Landsteiner's demonstration, some 20 years ago, that guinea pig skin can be sensitized to various compounds, skin sensitization has been studied extensively. The guinea pig has continued to be the animal of choice in such experimental procedures. Landsteiner's intracutaneous method, subsequently modified by Draize, has been employed with a fair degree of success in the food, drug, and cosmetic work carried out by the testing and research units of the Food and Drug Administration. It has been our experience that substances which sensitize the guinea pig are invariably capable of causing a similar effect in man. The weakness of the method lies in the fact that some substances, classed as nonsensitizers on the basis of this test, are later found to cause sensitization in man. Its greatest value would seem to be as a screening test to eliminate most of the sensitizers prior to human experimentation. A theoretic disadvantage of the method is the route of sensitization, since most compounds eliciting eczematous dermatitis do so as a result of repeated or continuous contact with the skin.

The Schwartz prophetic patch test is still widely used in screening compounds as potential sensitizers and employs human beings as the experimental subject. The method consists of a single exposure applied as a patch and remaining in contact with the skin for 48 hours to five days, followed by a single challenge patch 10 to 14 days later. This test is considered inadequate because only the most powerful sensitizers are capable of producing a response following a single exposure.

The Food and Drug Administration is of the opinion that a more suitable method of procedure is needed to determine the sensitizing power of new agents. At present, the Skin Toxicity Branch, in addition to its routine investigation and evaluation of new products, is conducting a full-time research program in the hope of either developing a new procedure for measuring sensitizing abilities of compounds, or improving one of the methods currently employed. While any new test must, of necessity, be designed for the evaluation of compounds that

might sensitize man, such a method should employ an experimental tool other than the human being. If animals are used, the test should be of such nature that compounds capable of sensitizing the animal evoke a similar response in man. The converse also must hold. Finally, exposure to the compound should include topical application rather than other routes of sensitization since most cases of eczematous dermatitis are of the contact type.

## Experimental Demyelination

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Destruction of the myelin sheath is a common pathologic feature of several diseases of the nervous system. It may or may not be accompanied by other changes of the neural elements.

The etiology of this destructive lesion is varied, and in some diseases it is unknown. Multiple sclerosis and Schilder's disease are examples of spontaneous demyelination occurring without apparent cause. On the other hand, some agents or factors that are known to have produced demyelination are potassium cyanide, arsphenamine, spinal anesthetics, saponins, and vascular lesions. A relatively new group of compounds, which are commonly referred to as organophosphorus cholinesterase inhibitors, may now be added to this list. They have much commercial value as insecticides, and as such they are of real concern to the Food and Drug Administration. As the grouping implies, they share at least two common characteristics, chemical similarity and the inherent capacity to inhibit the activity of the enzyme, cholinesterase.

The once familiar "ginger" paralysis of the early 1930's was attributed to demyelination of motor nerve fibers by triorthocresyl phosphate, a member of the group. This compound was present as an adulterant in certain samples of fluid extract of ginger that was used as an alcoholic beverage. The probability of the occurrence of "ginger" paralysis from triorthocresyl phosphate is of little concern today; however, paralysis in man has been reported following accidental poisonings by other members of this group. Although all of the organophosphorus compounds have not been used commercially as insecticides, their high order of toxicity has promoted the extensive use of some members of the group for this purpose. Therefore, the ingestion of food containing toxic levels of these insecticide residues that may be capable of producing paralysis is of major importance.

While it has been suggested that demyelination may result from inhibition of cholinesterase activity, present data do not support this hypothesis. However, it is noteworthy that the organophosphorus compounds producing demyelination also are inhibitors of cholinesterase activity.

The chicken appears to be the best test animal for screening the members of this group for the production of paralysis. Those compounds that have caused

paralysis in man following accidental poisonings have also produced paralysis in chickens. There is no index of the relative sensitivity of man and the chicken to paralysis by the organophosphorus insecticides.

It is known, for instance, that following the repeated administration of small doses of these enzyme inhibitors, a cumulative effect occurs that results in progressive inhibition of cholinesterase activity. In the study of demyelination in chickens by these insecticides, most investigators have made use of lethal or near lethal dosages. Death, or the symptoms of acetylcholine accumulation, were prevented by the previous administration of atropine. Paralysis usually followed in 10 to 14 days. The time of onset of paralysis is comparable to that which was found in the cases of "ginger" paralysis in man. Preliminary findings from the Food and Drug Administration research laboratories indicate that paralysis may be produced in chickens by repeated small doses of these enzyme inhibitors. The paralysis, although more delayed, is as striking as that produced by triorthocresyl phosphate. This points out that the effect on the myelin sheath may be cumulative, as is the effect of cholinesterase activity. Additional experimental work on the degree of cumulation and the mechanism of production of paralysis will reveal the importance of this observation on the potential toxicity of these insecticide residues to man.

The Food and Drug Administration has the responsibility of establishing a safe residual tolerance for each insecticide that is to be used on food. By taking the assumption that man is more susceptible to neural damage than any other species and utilizing the experimental data of the manufacturer, the literature, and our own research laboratories, tolerances are established that provide an adequate margin of safety.

## Drug Metabolism—An Index of Toxicity

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The science of pharmacology today is in a state of transition. This statement is not limited to pharmacology alone but is applicable to all biologic sciences in general and to toxicology, which is but a branch of pharmacology, in particular. This transition is a change from a purely descriptive science to a true experimental science that allows for the prediction and control of the effects under study. In terms of toxicology, this means that the tests for the evaluation of a substance are evolving from a practice of administering the experimental compound to laboratory animals and counting the number that die, toward a more exact science in which the toxicologist can predict the effect of the compound upon the body, and by knowing the mechanism by which the damage is effected can control it.

The purely ratiocinative approach to toxicology is not yet possible. In fact, it is probably not possible within the foreseeable future; however, in order to

carry out its duties in protecting the nation's health through the evaluation of the safety of drugs, foods, and food additives, the Food and Drug Administration is making continuous progress in this direction. Among the approaches being pursued are those involving pathology, cytochemistry, and histochemistry; studies of physiologic and biochemical function and dysfunction of the body; investigations into the mechanisms of the action of drugs at both the cellular and the molecular level; and the study of drug metabolism.

Drug metabolism in its broadest sense may be defined as all chemical changes and reactions in which the drug participates directly within the body. This would include such topics as protein binding and the reaction of the drug with its receptor site and would lead ultimately to the study of the mechanism of the action of drugs at the molecular level. The field is thus too broad for this discussion and must be limited. As used here, drug metabolism may be defined as the chemical changes in the drug itself within the body, the distribution of the drug and its metabolites or products of chemical change, and the rate and route of their excretion.

The toxicity of a compound is not only dependent upon the toxicity it may possess per se, but also upon the length of time it remains in the body, the rate of its excretion, the rate and site of its biotransformation, and the toxicity of the products of metabolism. All of these points are aspects of the study of drug metabolism. The length of time a foreign compound remains in the body is, of course, a function of its rate of excretion and its rate of biotransformation or detoxication.

What information can be obtained from a distribution excretion experiment that cannot be obtained from a program of dosing animals and observing any toxic effects? The answer to this must be divided into two main parts according to the use intended for the drug. If it is a substance intended for human consumption, distribution-excretion data will show if the compound is stored in the body, perhaps at levels so low as to have no immediate effect but only a cumulative effect apparent after many years. The route of excretion will indicate possible contraindications for the use of the substance. A substance excreted by the kidney might be safe for consumption by a healthy individual but would be dangerous in a person with kidney function impairment.

It is with substances not intended for human consumption but for use in domestic animals used as food sources that the distribution-excretion information is most useful at the present time. A compound that, when fed to meat animals, appears in the flesh is potentially dangerous and must be toxicologically evaluated. Similarly, such a chemical might appear in milk of dairy animals. This again is potentially dangerous and would require the most careful investigation. However, if a material is found to be completely nonabsorbed, or if the amount that is absorbed can be shown to be entirely in the chemically altered form of a natural body constituent, there would be no danger of human consumption of the milk or meat of a treated animal.

The actual detoxication mechanism holds the greatest potential to toxicology. The more obvious applications of this are in wide use today. The site of detoxica-

tion is quite important. If a toxic chemical is altered to a less toxic compound in an organ such as the liver, a dysfunction of that organ might greatly increase the toxicity of the poison. Contrariwise, the fact that a substance is metabolized in a certain organ suggests a possibility that damage to that organ might occur. A further point to be raised in this regard is the toxicity of the products of metabolism. Although these reactions are generally called detoxication reactions, that does not mean that the product is less toxic, occasionally it is more so. A striking example is seen in the case of octamethylpyrophosphoramide. This compound itself is relatively nontoxic, and when administered to animals having no "detoxifying" mechanism equivalent to the liver, there is no damage. However, in the mammal, this compound is transformed into an extremely toxic poison. In this case, impaired liver function would tend to decrease the toxicity of octamethylpyrophosphoramide rather than to increase it.

A final application of detoxication mechanisms to the science of toxicology is to be found with species variations. The primary rationale for the use of several species in toxicity evaluation is the difference in metabolism or detoxication among species. If one knows the mechanisms involved in the detoxication of a compound and the differences in the capabilities of these mechanisms between man and the laboratory animals, the extrapolation of data obtained with animals to what might be expected with man can be done much more intelligently.

## Carcinogenic Substances in Foods

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This editorial is written neither by nor for an expert cancer worker. Instead, it is written by a general pathologist for the general medical reader.

With the (1) ever-increasing tendency toward "chemicalization" of foods, (2) the increased number of minute amounts of contaminating chemicals such as pesticides, and (3) the increasing tempo of cancer research, the possible role of the diet and its contaminants in relation to cancer has an understandable interest. The term "chemicals" in relation to food is a reasonable one. True, food was composed of chemicals even in primitive days, but in everyday language "chemical" refers to the more purified and synthetic components and contaminants of food rather than to the naturally occurring chemical agglomerations present.

It should be noted immediately that the subject "carcinogenic substances in foods" is a much less inclusive one than "nutrition and cancer." The former, in a strict sense, leaves out consideration of the cancer itself, dietary influence on a cancer after it has become established, and dietary influence in restraining the potential activity of endogenous carcinogens and endogenous aiding factors. This brief discussion will hold rather closely to its title; in other words, it concerns cancer from nutrition rather than nutrition affecting cancer.

Does the diet, with its possible carcinogenic content, influence the incidence of human cancer? About this we know essentially nothing because of the lack of the necessary statistical data and because of the multiplicity of factors involved. Once human cancer is established, dietary influence of any consequence upon it is not known. In contrast, the incidence of certain animal tumors, particularly the rat liver tumors caused by azo compounds, is highly influenced by dietary variations, and once established, animal tumors are still influenced. It should be understood that caloric variation is included in the term "dietary variation."

Specifically, then, as to actual substances: Heated (and overheated) fats, and to a lesser extent roasted foods, have been among the most studied food items with respect to experimental cancer production. While they have often been heated to a greater degree than would normally occur, this is a reasonable trial technique. The important point, however, is whether there has been a definite production of cancer by the feeding of such substances. It is at least an open question. A careful reading of the published evidence leads to the reasonable conclusion that the amount claimed is greater than the amount not accounted for by parasitism, chance occurrence, or malnutrition. By the nature of the treatment of the food item, it is most difficult or even impossible to have a material that differs from the untreated material only by the presence of a single chemical compound. In some experiments, the feeding of heated fat has been complicated by the additional feeding of such substances as croton oil, pepper, or soap. Even subcutaneous injection of heated fat, the control animals being injected with unheated fat, does not get away from variables; there are physical differences, such as viscosity, that can affect the results, and greater retention of heated fat than of unheated fat at injection sites has been noted. It would seem that heated fat feeding studies may be summarized by saying that a low grade of tumor production has occasionally been achieved. More important, and only beginning, is the chemical characterization of the responsible agents, and the realization of how seemingly insignificant differences in treatment (e.g., heating in an iron as contrasted to a glass container) may change the character of the heated material.

Considerable concern has been expressed about the possibility of colors and insecticide residues in food being carcinogenic. A minimal degree of liver tumor production in rats is known for dichlorodiphenyltrichloroethane (DDT) and certain other insecticides. However, the amounts needed to do this are much greater than the amounts ingested as residue by man, and, because of this safety factor, the minimal degree of rat tumor production is not alarming. However, when an insecticide is a distinct tumor producer, as for example selenium, the situation is different.

The only food colors considered here are the 19 certifiable Food, Drug, and Cosmetic colors used for food coloring in the United States. None of these has as yet shown evidence of carcinogenicity in man or in feeding tests with experimental animals. Some, particularly in the triphenylmethane class, have produced fibrosarcomas at the site of repeated subcutaneous injections in rats. This site, known to be a sensitive one and only recently coming into common use in carcinogenicity testing, is of course an abnormal one as far as food colors in the diet are

concerned. To the extent that time and limited facilities permit, the Food and Drug Administration is engaged in more detailed animal toxicity studies with these colors than has heretofore been done. Partially as a suggestion to other researchers who are concerned with possible food color carcinogenicity, it should be noted that five of the 19 colors together account for more than 80 per cent of use, and eight of them together account for less than 2 per cent of use.

Has any single carcinogenic substance been isolated from "natural," uncontaminated human foods? The answer must yet be "no," because although certain foods (chili peppers, Hoch-Ligeti; buckwheat, Kubo et al) have caused liver tumors in rats and mice respectively, the tumor formation has not been shown to be dependent upon a single chemical substance. The "uncontaminated" leaves out crude ergot, a contaminant of rye, which caused neurofibromas of the ears in rats (Nelson et al).

Substances that have been found to be carcinogenic (rat liver tumors) in recent years, and that for that and other reasons the Food and Drug Administration has tried to keep out of foods, include dulcin, thiourea, and compounds of selenium. These were, respectively, a synthetic sweetener, a preservative, and insecticides. As new chemicals and new uses for old ones are developed, some of these will no doubt also be found carcinogenic.

The foregoing has presented some of the highlights in a complex and many-faceted problem.

## The Antibiotic World

The miraculous world of antibiotics continues to grow, and the end is nowhere in sight. At last November's Third Annual Symposium on Antibiotics,* 12 new antibiotics were announced, new uses were found for some of the older ones, and also reported was a new form for oral use of penicillin, that sturdy clinical standby.

This new phenoxymethyl penicillin, called penicillin V, was in fact one of the highlights of the symposium. Clinicians from this country and Europe reported that they had obtained high blood levels of the antibiotic with oral doses, although the over-all activity of penicillin V and the standard penicillin G appeared to be about the same. The crucial difference seems to lie with the patient who protests against frequent injections; on the other hand, some patients may be unable to swallow any medication. The discussions brought out at least one valuable "side effect," namely, that it is high time the astronomic calculations of penicillin dosage in units be dropped in favor of the simple gram system—1 Gm. equals 1,600,000 units. The shade of Alexander Fleming, who liked simplicity above all, would certainly welcome the change.

The other report in which unusual interest was shown concerned streptomycin. Basing their work on the premise that streptomycin sulfate can cause vestibular dysfunction and dihydrostreptomycin may impair hearing, a group of German clinicians reported that these side effects could be considerably reduced by combining streptomycin with calcium pantothenate. They showed an interesting film purporting to demonstrate this finding in cats, but a good deal more research will need to be done before their point is conclusively proved.

Among the new antibiotics active against gram-positive organisms that made their bow were cathomycin, spiramycin (France), streptolydigin, PA 114, and thiostrepton. Against gram-negative bacteria and staphylococci we had soframycin, while others with a varied spectrum included rubidin (India), streptonivicin, and vancomycin. New agents against the troublesome fungi were two forms of amphotericin, eulicin, and the unnamed no. 1968.

Good reports were heard about cycloserine, the antibiotic that made its debut in 1955 and is still something of a paradox. It is active against the tubercle bacilli in vitro but relatively inactive in protecting the usual laboratory animals, and yet it gives good results in treating human tuberculosis. According to French clinicians, it can in some cases be compared with isoniazid. Other preliminary reports mentioned encouraging results in the treatment of urinary tract infections and a variety of nontuberculous infections. More will undoubtedly be heard about this antibiotic.

In the discussions on the widely used antibiotics, such as the "cycline" group, less was heard at the symposium about the bogey of microbial resistance. That certain germs do develop resistant strains is undoubted, but it is by no means certain whether this power of resistance will not diminish in coming years. Moreover, as the number

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## TABLE OF NEW ANTIBIOTICS

*Presented at the Third Annual Symposium on Antibiotics*
*Washington, November 2, 3, and 4, 1955*

| Name | Source | Activity |
|---|---|---|
| Amphotericin (A and B) | Broths inoculated with streptomycetes culture | Wide variety of fungi and *Candida albicans* |
| Cathomycin* | *Streptomyces spheroides* | Gram-positive bacteria, especially *Micrococcus pyogenes* var. *aureus*. Some gram-negative bacteria |
| Streptonivicin* | *Streptomyces niveus* | *Micrococcus pyogenes* var. *aureus*, *Streptococcus hemolyticus*, *Diplococcus pneumoniae*, *Proteus*, *Pasteurella multocida*, *Salmonella typhosa*, and *Klebsiella pneumoniae* |
| Eulicin | Species similar to *Streptomyces parvus* | High against majority of cutaneous and systemic fungi, low against *Candida albicans* |
| Rubidin | Species similar to *Streptomyces griseus* and *Streptomyces coelicolor* | *Staphylococcus aureus*, *Bacillus subtilis*, *Vibrio cholerae*, *Mycobacterium phlei*, *Mycobacterium avium*, *Salmonella typhosa*, *Escherichia coli* |
| Soframycin | *Streptomyces lavendulae* | Gram-negative bacteria and staphylococci |
| Spiramycin† | *Streptomyces ambofaciens* | Broad spectrum against gram-positive bacteria and *Neisseria* |
| Streptolydigin‡ | *Streptomyces lydicus* | Gram-positive bacteria, especially clostridia, mycobacteria, *Pasteurella multocida*, and *Nocardia asteroides* |
| PA 114 (two distinct chemical entities, A and B, with synergistic action) | Strain similar to *Streptomyces olivaceus* | Wide variety of gram-positive organisms |
| Thiostrepton | Unclassified species of *Streptomyces* | Gram-positive organisms, particularly cocci, and penicillin-resistant *Micrococcus pyogenes* var. *aureus* |
| Vancomycin§ | *Streptomyces orientalis* | *Streptococcus pyogenes*, *Micrococcus pyogenes* var. *aureus*, *Diplococcus pneumoniae*, *Borrelia novyi* |
| No. 1958 | *Streptomyces aminophilus* (tentative) | Wide variety of fungi, especially *Candida* and *Cryptococcus neoformans* |

* From studies done by the Division of Antibiotics, Food and Drug Administration, Department of Health, Education, and Welfare, it was determined that the two new antibiotics, cathomycin and streptonivicin, are identical. The trade name of The Upjohn Co. for streptonivicin is Albamycin.

† The trade name of Rhône-Poulenc for spiramycin is Rovamycin.

‡ The trade name of The Upjohn Co. for streptolydigin is Portamycin.

§ The trade name of Eli Lilly & Co. for vancomycin is Vancocin.

of available antibiotics increases and new combinations and permutations are tried out, we may in the long run outstrip the ability of bacteria to protect themselves by genetic mutation. The panel of experts who discussed this subject at the symposium were commendably cautious about foretelling the future.

The latest development in antibiotic therapy—the combination in one formula of a broad-spectrum antibiotic and a selection of vitamins and minerals—was well received at the Symposium. The body's need for certain vitamins and minerals is increased during the stress of disease, a fact that is still lamentably overlooked in a number of hospital diet routines. Any form of medication that enlists the organism's natural defenses is to be encouraged.

One pharmaceutical firm announced that fresh meat could be kept for days without refrigeration if animals were injected with oxytetracycline before being slaughtered. This should be of particular interest to such countries as England that have to import most of their meat. Broad-spectrum antibiotics were also praised for their ability to reduce the incidence of mastitis and atrophic rhinitis in livestock.

The Symposium, held in the green marble halls of the Department of Health, Education, and Welfare in Washington, D. C., was truly international in character. Speakers were heard from Austria, Australia, Germany, France, South Africa, Japan, Mexico, Canada, Sweden, Denmark, Spain, and Portugal. The supranational character of Medicine was in full flourish. At the forthcoming Fourth Symposium this year, who can say what new marvels will be launched?

Papers of special interest, presented at the Third Annual Symposium on Antibiotics, are abstracted below and on the following pages.

## Amphotericins A and B, Antifungal Antibiotics Produced by a Streptomycete. I. In Vitro Studies

Presented by W. Gold, H. A. Stout, J. F. Pagano, and R. Donovick, Squibb Institute for Medical Research, New Brunswick, N. J.

From broths inoculated with a streptomycete culture isolated from soil, two antifungal materials, amphotericins A and B, have been isolated. Amphotericin A resembles the tetraene antibiotics nystatin and rimocidin, whereas amphotericin B is similar to the heptaenes ascosin and trichomycin. The culture will be described.

The antibiotics are insoluble in water but are soluble in aqueous alcohols, with which they are extracted for assay. Dilution assays in broth are made against *Saccharomyces cerevisiae* as indicator organism.

Amphotericin B is several times more active than amphotericin A against yeasts and yeastlike fungi, so that dilution assays of mixtures reflect the content of B. In agar diffusion assays, the sizes of zones of inhibition are independent of the concentration of B but vary with the content of amphotericin A. At present, physical and chemical methods of assay are used together with biologic methods to determine amounts of A and B in mixtures.

Amphotericin A resembles nystatin in biologic activity, both in its broad spectrum and in its minimal inhibitory concentrations. Amphotericin B differs from A in its

spectrum and in minimal inhibitory concentrations, resembling the antibiotics ascosin and trichomycin.

Neither antibiotic is active against bacteria. Both will protect mice against lethal infections with *Candida albicans* and other fungi.

## The Next Half Century in Antibiotic Medicine and Its Impact on the History of the Clinical Case History

Presented by Félix Martí-Ibáñez, M.D., International Editor of *Antibiotics & Chemotherapy* and Associate Editor of *Antibiotic Medicine*, New York, N. Y.

The change in the character of clinical case histories reflects the profound changes in the history of medicine. The author analyses the six factors that today determine the clinical case history of infectious patients, and projects these into the possible modifications that may arise within the next half century or so.

The first element is the changing concept of disease as a mere microbial entity to be destroyed by chemotherapeutic agents, without much regard for the patient as a whole. The second aspect is the tendency to regard disease as a group of concomitant factors rather than to seek a single etiologic cause. A third aspect is the recognition that man must come to terms with the world's microbes. The fourth will be the development of antibiotics with specific antimicrobial activity. The fifth factor of change will be the altered environment caused by the prolongation of life, and the sixth will be the overall integration of medicine with other branches of knowledge and culture.

The author makes the point that medicine in the year 2000 will be more prophylactic than therapeutic, with attempts being made to prevent disease by providing human beings with scientifically designed diets and salubrious living conditions. What is today called antibiotic medicine will by then have developed into an antibiotic science. To hasten this change, the author pleads for the establishment of an International Institute of Antibiotics and Chairs of Antibiotics in universities.

## The Biologic Activity of Eulicin

Presented by Margaret King West, W. F. Verwey, and A. Kathrine Miller, Department of Bacteriology, Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa.

Eulicin, a new antifungal antibiotic agent, has been examined in vitro for its activity against a number of pathogenic fungi and in vivo against a *Blastomyces dermatitidis* infection in mice. The in vitro spectrum showed a high level of activity against the majority of both the cutaneous and systemic fungal pathogens, with the exception of *Candida*, where the activity appeared to be considerably lower. This antibiotic agent was fungicidal to a culture of *Cryptococcus neoformans* at five times the fungistatic level as measured by broth dilution techniques.

The activity of eulicin in vivo against a *B. dermatitidis* infection of mice, when administered either intraperitoneally or intramuscularly, was much greater than the

activity of stilbamidine and 2-hydroxystilbamidine when the dosage was calculated on the basis of weight. Unlike most of the other known systemic antifungal agents, eulicin also appeared to be active when given by the oral route of administration. The amount of this antibiotic agent required to protect 50 per cent of the infected mice was well below the toxic level by all three routes.

## A New French Antibiotic: Spiramycin

Presented by A. Ravina, M. Pestel, Ph. Eloy, and G. Duchesnay, Hôpital Beaujon, Clichy, France.

With a 10 month follow-up, we have clinically investigated a new antibiotic: spiramycin, produced by a strain of *Streptomyces ambofaciens*. Chemical, biologic, and animal studies have already been communicated by Pinnert-Sindico et al at the Second Annual Symposium on Antibiotics. Spiramycin is a broad-spectrum antibiotic, mainly effective against gram-positive bacteria and *Neisseria*. Its activity is stronger in vivo than in vitro. Spiramycin is mostly used orally at an average daily dose of 3 Gm., which can be increased to 5 Gm. and reduced to 2 Gm. for a prolonged administration. We have also given spiramycin intrapleurally or locally in a lyophilized solution. Very good results have been obtained in the treatment of pneumopathies, especially in the pneumonia of old age, pyothorax, pulmonary chronic suppuration, and bronchiectasis. This antibiotic is efficacious against acute tonsillitis, infectious endocarditis, and, principally, in staphylococcal conditions. We have treated successfully cutaneous infections, infected wounds, furunculosis, panaris, and carbuncle very quickly and without surgery. It looks as if spiramycin will start a new development in the treatment of staphylococcal conditions.

## Preliminary Report on Bowel Sterilization with Soframycin

Presented by Boris A. Shidlovsky, Milton Marmell, and Aaron Prigot, Departments of Surgery and Pathology, Harlem Hospital, Department of Hospitals, New York, N. Y.

Soframycin, a new antibiotic, isolated from *Streptomyces lavendulae*, has been shown to have antimicrobial, but not fungicidal, activity. Its action is not only bacteriostatic but also bactericidal and the bactericidal concentration is similar to that required for bacteriostatic inhibition. This antibiotic is effective against a wide variety of organisms, especially the staphylococci and the gram-negative group.

On parenteral administration, serum concentrations are obtained that are well above those required to inhibit a large variety of pathogenic organisms. On oral administration, low serum concentrations are detected, but marked levels are noted in the urine.

Because of its activity against the gram-negative organisms, it was decided, as a preliminary study, to evaluate the effect of soframycin upon the bacterial population of the intestinal tract of man.

On oral dosages as low as 1 Gm. of soframycin daily, there was a reduction in the

total bacterial count and a marked decrease in the gram-negative population, with little effect on the gram-positive organisms (enterococci).

We have observed no toxic reactions to oral administration of the antibiotic.

This preliminary trial indicates that soframycin has a place in the treatment of bacterial infections of the intestinal tract of man and in the presurgical preparation of the large bowel.

## Rubidin, a New Antibiotic Pigment from a *Streptomyces* sp.

Presented by A. K. Banerjee, G. P. Sen, and P. Nandi, Microbiological Laboratory, Bose Institute, Calcutta, India.

A red antibiotic, rubidin, was isolated from the culture filtrate of a strain of *Streptomyces* by solvent extraction and countercurrent distribution. The antibacterial spectrum (μg./ml.) of the substance, obtained as a red powder, is as follows: *Staphylococcus aureus*, 1 to 2.5; *Bacillus subtilis*, 1 to 2.5; *Vibrio cholerae*, 1 to 2.5; *Mycobacterium phlei*, 5 to 10; *Mycobacterium avium*, 5 to 10; *Eberthella typhosa*, 62.5 to 100; and *Escherichia coli*, 100.

The compound is soluble in most organic solvents, slightly soluble in sodium and bicarbonate, and insoluble in water and petrol ether. It is unstable at *p*H above 8.0. The compound is red when acidic, violet when neutral, and blue when alkaline.

When treated with sodium bisulfite, as well as with zinc dust and dilute acetic acid, the red color is discharged to reappear again on aeration. The substance gives positive ferric chloride test.

The dried preparation analyses: C, 51.9; H, 5.56; and 0, 42.54. It shows absorption maxima at 500, 530 μ in (0.1 *N*) hydrochloric acid; at 400, 520 μ in (0.1 *N*) sodium hydroxide; at 320, 415, and 490 μ in *n*-butanol; and at 530 μ in concentrated sulfuric acid. The infrared spectrum indicates the presence of bonded hydrogen and carbonyl groups.

Paper chromatographic studies with six solvent systems demonstrate the homogeneity of the substance and its distinction from related compounds.

Morphologic and cultural characteristics of the antibiotic-producing organism are compared with *Streptomyces griseus* and *Streptomyces coelicolor*.

## Streptolydigin, a New Antimicrobial Antibiotic III. In Vitro and In Vivo Laboratory Studies

Prepared by C. Lewis, J. R. Wilkins, D. F. Schwartz, and C. T. Nikitas, Research Laboratories, The Upjohn Co., Kalamazoo, Mich.

The biologic properties of a new antimicrobial antibiotic, streptolydigin, are described. The antibiotic is active in vitro and in vivo (mouse) primarily against gram-positive bacteria, including strains of streptococci, diplococci and clostridia. It was inactive against micrococci in a range of 25 to 100 μg./ml. It inhibits *Pasteurella multocida* but has no effect against some gram-negative bacteria at 100 μg./ml.

The optimal *p*H for streptolydigin activity is near neutrality in broth. Cysteine

(0.01 *M*), methionine (0.01 *M*) or penicillinase did not affect the in vitro activity of the antibiotic. Some serum binding with 10 and 20 per cent human and horse serum was demonstrated.

Streptolydigin is not cross resistant with other antibiotics. Resistance develops at a rapid rate, similar to that for streptomycin.

The maximum tolerated levels of sodium streptolydigin for seven days were 400 mg./Kg./day by subcutaneous route and 1000 mg./Kg./day by oral route. Streptolydigin free acid was tolerated subcutaneously at 500 mg./Kg./day and orally at 1800 mg./Kg./day.

## Streptonivicin: Laboratory and Clinical Studies in the Pediatric Age Group

Presented by Feng-Kai Lin and Lewis L. Coriell, Camden Municipal Hospital, Camden, N. J.

Streptonivicin is an antibiotic produced by *Streptomyces niveus* n. sp., an actinomycete isolated from a soil collected in Queens Village, N. Y. It is reported to be active in vitro and in vivo against *Micrococcus aureus*, *Streptococcus hemolyticus*, *Diplococcus pneumoniae*, *Proteus vulgaris*, *Pasteurella multocida*, *Salmonella typhosa*, and *Klebsiella pneumoniae* infections.

The purpose of this paper is to show the potential usefulness of this drug in treating infections caused by *M. pyogenes* var. *aureus*, as follows: bacteriostatic and bactericidal concentrations of streptonivicin on *M. pyogenes* var. *aureus* no. 209 have been determined in broth culture. Penicillin, chloramphenicol, and erythromycin were used as controls.

Cross resistance was determined by serial transfer of *M. pyogenes* var. *aureus* no. 209 in streptonivicin, penicillin, chloramphenicol, and erythromycin solutions until resistance was established. The resistant strain was then checked for its sensitivity to the other three antibiotics. There is little cross resistance as shown by this test. The resistance to streptonivicin develops at a stepwise rate similar to erythromycin.

Different strains of micrococci collected from patients in the hospital were tested for their sensitivities against streptonivicin, using penicillin, chloramphenicol, and erythromycin as controls.

## The Isolation of Two Synergistic Antibiotics from a Single Fermentation Source

Presented by Walter D. Celmer and Ben A. Sobin, Research Laboratories of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

A strain of *Streptomyces* resembling *S. olivaceous* elaborates two new antibiotics recoverable together from fermentation filtrates by solvent extraction. The antibiotics were separated by differential solvent solubility, purified by countercurrent distribution, and crystallized. Mixtures of the crystalline antibiotics exhibited more activity against gram-positive bacteria than expected of a simple algebraic summation in both in vitro and in vivo studies. These new antibiotics are designated "PA 114 A" and "PA 114 B."

PA 114 A is a neutral compound, $C_{28}H_{31}N_3O_6$ (an alternate molecular formula $C_{35}H_{42}N_4O_9$ cannot be definitely excluded at this time). PA 114 A crystallizes as colorless needles from n-butylethyl ketone, m.p. 200 C. (dec.), $[\alpha]_D^{25}$–207° (c, 0.5 methanol) and gives a green ferric chloride test.

PA 114 B is an acidic compound, $C_{52}H_{62}N_6O_{12}$, neutral equivalent, 1000, pKa 8.5. The antibiotic crystallizes as colorless tablets from methanol and as feathery needles from toluene, m.p. 265 C., $[\alpha]_D^{25}$-59.7° (C, 0.5 methanol) and gives a red ferric chloride test.

## Thiostrepton: A New Antibiotic III. In Vivo Studies

Presented by Bernard A. Steinberg, William P. Jambor, and Lyda O. Suydam, with the technical assistance of Mrs. A. Soriano, The Squibb Institute for Medical Research, New Brunswick, N. J.

A new antibiotic from an unclassified species of *Streptomyces* has been isolated in the laboratories of the Squibb Institute for Medical Research. This antibiotic, thiostrepton, is active primarily against members of the gram-positive group of organisms, particularly the cocci.

We have repeatedly demonstrated activity against streptococcal infections in mice. The $PD_{50}$ in these infections is less than 10.0 μg. when given by the subcutaneous route. Given intravenously, the drug has a $PD_{50}$ of less than 5.0 μg.

Thiostrepton has also demonstrated a lack of cross resistance when used to treat infections in mice with staphylococci resistant to a number of commonly used antibiotics, including penicillin.

We have also shown that thiostrepton has a moderate effect on the course of infection with *Ricksettsia ricksettsii* and meningopneumonitis virus in embryonated eggs.

We have used the crystalline antibiotic with good results in our tests in mice. When the material is prepared so that it is amorphous in the physical state, then the activity is increased to a large extent. The amorphous material suspends easily in water and is effective by both the subcutaneous and intramuscular routes.

The high ratio of toxicity to activity indicates that thiostrepton is an antibiotic with clinical promise.

## Vancomycin, a New Antibiotic I. Chemical and Biologic Properties

Presented by M. H. McCormick, W. M. Stark, G. E. Pittenger, R. C. Pittenger, and J. M. McGuire, The Lilly Research Laboratories, Eli Lilly Co., Indianapolis, Ind.

The production and properties of a new antibiotic, vancomycin, that is active against a variety of gram-positive organisms and spirochetes are described.

Vancomycin is produced by a new species of the *Streptomyces* genus, *Streptomyces orientalis*. It is an amphoteric compound soluble in dilute acidic solutions and relatively insoluble in the lower alcohols and other common organic solvents.

The in vitro activity of this antibiotic is characterized by a lack of development of resistance in strains of *Micrococcus pyogenes* var. *aureus* and by the ability to inhibit all available antibiotic-resistant strains of this organism.

Vancomycin affords protection to mice infected with *Streptococcus pyogenes*, *M. pyogenes* var. *aureus*, *Diplococcus pneumoniae* type I, and *Borrelia novyi*.

Toxicity studies have indicated a low acute toxicity (when administered intravenously); no indication of deleterious manifestations were observed following repeated administration over a longer period of time.

Preliminary data have shown that vancomycin is clinically effective in several diseases caused by gram-positive organisms.

## Therapeutic Activity of a New Antibiotic, 1968, in Mice with Experimental Histoplasmosis, Sporotrichosis, and Moniliasis

Presented by C. C. Campbell, Grace B. Hill, and B. Brooks, Department of Bacteriology, Army Medical Service Graduate School, Washington, D. C.

Preliminary studies with an antibiotic derived from *Streptomyces* sp. 1968 (Nepera) reveal that this drug has a markedly beneficial effect on the course of experimental moniliasis, histoplasmosis, and sporotrichosis in mice.

In mice infected with *Sporotrichum schenckii* and treated with a total dosage of 10 mg. crude drug (lot 5), 70 per cent survived a 28 day observation period in contrast to a 100 per cent mortality in untreated controls. In a second experiment with moniliasis and a total dosage of 15 mg. (lot 12), 80 per cent of the treated animals survived as compared to a 95 per cent mortality in the untreated group. Against *Histoplasma capsulatum* the drug was less effective. Nevertheless, a 20 mg. total dosage (lot 5) protected 65 per cent of the treated mice from an infective dosage that by the fourteenth day produced a 90 per cent mortality in the untreated controls.

More recent studies indicate that the lots of drug employed in these studies were extremely crude. With a third and more highly purified preparation of antibiotic 1968 (lot 98), a total dosage of as little as 2.5 mg. protected 80 per cent of the mice infected with *Candida albicans* for a period of more than 60 days. In the latter experiment, the drug appeared to be fungicidal.

These preliminary findings suggest that this antibiotic warrants further investigation as a potential chemotherapeutic agent for the systemic mycoses in man.

## The Pantothenates of Streptomycin, Viomycin, Neomycin, New and Less Toxic Salts

Presented by H. Keller, W. Krupe, H. Sous, and H. Muckter, Chemie Grunenthal GMBH, Stolberg im Rheinland, Germany.

The basic *Streptomyces* antibiotics have two characteristics in common: their tuberculostatic effect and their ototoxicity. In the case of streptomycin, two principles have proved to enhance tolerability.

(1) After the transformation from streptomycin into dihydrostreptomycin, the acute toxicity has been changed about half the time. Unfortunately, regarding the chronic toxicity, the prolonged use of dihydrostreptomycin was associated with the occurrence of cochlear damages—from the social aspect more serious—instead of the vestibular disturbances known from streptomycin. The ingeniously simple suggestion of Heck and Hinshaw to use mixtures of both these streptomycins which, as regards chronic toxicity, constitutes a genuine progress but a certain regression from the acute toxicity point of view—as compared with dihydrostreptomycin—is based on this different localization.

(2) A new situation emerged as soon as it was found that pantothenic acid reduces the acute as well as the chronic neurotoxic side effects of the basic *Streptomyces* antibiotics without affecting the latters' antibiotic activity. The pantothenates, consequently, increase the therapeutic index. While, with regard to acute tolerability, dihydrostreptomycin pantothenate is the preparation of choice, the mixed pantothenates can be considered to be more favorable as far as chronic toxicity is concerned.

Similar results were obtained with using the pantothenates with viomycin and neomycin.

A film was used to show that the pantothenates mean more than a pure substitution therapy, since the lack of pantothenic acid does not give rise to eighth nerve damages. On the other hand, these specific disturbances due to streptomycin can be reduced by pantothenic acid. The discovery that pantothenic acid is the detoxicating principle for the basic *Streptomyces* antibiotics constitutes a special example stressing the close connection between antibiotics and vitamins in metabolism.

## Serum Penicillin Concentration Following Oral Administration of Penicillin V

Presented by Herbert Linden, Sydney Finegold, and William L. Hewitt, Departments of Medicine, University of California Medical School and Veterans Administration Center, Los Angeles, Calif.

Capsules containing 200,000 units of penicillin V and commercial 200,000 and 500,000 unit tablets of penicillin G were administered to adults with no evidence of cardiac, renal, or hepatic disease. Penicillin was administered with respect to meals. Serum penicillin concentrations were determined by the *Sarcina lutea* disc plate method and serial twofold tube dilution technique. Zone diameters with the plate method were somewhat smaller with penicillin V than G and were usually not obtained at concentrations of 0.03 units/ml.

Mean serum concentrations at one-half, two, four, and eight hours following doses of 400,000 units of penicillin G were 1.0, 0.88, 0.38, and 0.16 units/ml., respectively; and, following penicillin V, they were 0.57, 1.46, 0.49, and 0.08 units/ml., respectively. Eight hours after administration, 12 of 15 patients receiving penicillin G had levels of 0.03 units/ml. or greater, contrasted with 6 of 12 patients receiving penicillin V.

Mean serum penicillin concentrations at the same intervals following 1,000,000

unit doses of penicillin G were 1.31, 1.19, 0.32, and 0.14 units/ml. and those following penicillin V were 1.83, 2.44, 1.3, and 0.27 units/ml. Twelve of 14 patients receiving penicillin G had levels of 0.03 or greater eight hours after administration as compared with 5 of 7 receiving penicillin V.

Penicillin concentrations of the serum samples were relatively stable in the case of both penicillin G and V at −20 C. but penicillin serum showed considerably more rapid deterioration than G at 10 C.

Additional pharmacologic data are being accumulated. Incidence of side effects will be presented.

## Discovery and Antimicrobial Properties of Cathomycin, a New Antibiotic Produced by *Streptomyces spheroides* n. sp.

Presented by HYMAN WALLICK, DALE A. HARRIS, MARY ANN REAGAN, MYRLE RUGER, AND H. BOYD WOODRUFF, Research Laboratories, Chemical Division, Merck & Co., Inc., Rahway, N. J.

A new antibiotic has been obtained from a species of *Streptomyces* isolated from soil. The antibiotic was differentiated from other known antibiotics by its antibacterial activity against various antibiotic-resistant microorganisms and its distribution properties on paper chromatograms. The antibiotic was first isolated in crystalline form by Kaczka, Rathe, and Folkers (Chemical Division, Merck & Co., Inc.). It is an acidic substance and has been named "cathomycin."

Cathomycin is produced by a microorganism different from any previously described. The organism has been named *Streptomyces spheroides*.

An agar diffusion assay for cathomycin has been developed employing a strain of *Bacillus subtilis*. Cathomycin is produced in media containing various complex nitrogenous materials and dextrose. The temperature of incubation is an important factor in determining the yield of cathomycin. The antibiotic has been produced in shake flasks and small laboratory fermentors for experimental purposes and larger quantities, sufficient to support clinical investigation, have been isolated from production-scale fermentors.

Cathomycin is active primarily against gram-positive bacteria and is especially active against strains of *Micrococcus pyogenes* var. *aureus*, including strains resistant to other clinically effective antibiotics.

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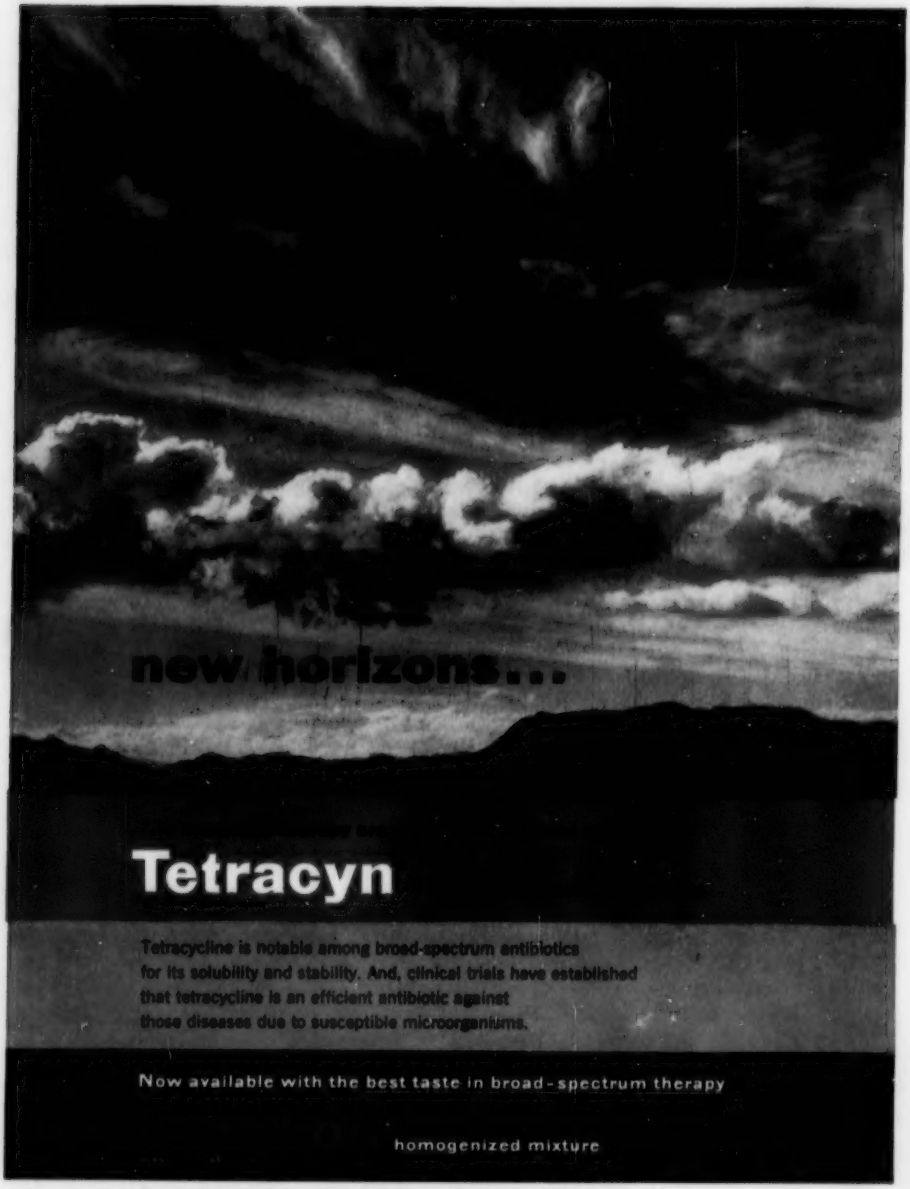
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